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CLOSING THE ABDOMINAL WALL IN HIGH-RISK ABDOMINAL SURGERY.

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Closing the abdominal wall in high-risk abdominal surgery.
THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

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The thesis will be defended in public at Hörsalen Capio S:t Görans sjukhus Stockholm, 2021-06-04 09.00

Zoom-meeting is available. Contact harald.soderback@ki.se or follow link https://ki-se.zoom.us/meeting/register/u50od-iurjgjHtMDmuVL-d1tR7nGt4RqZZVH

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To my family, Elin, Tove and Karin

POPULAR SCIENCE SUMMARY OF THE THESIS

Wound dehiscence and Incisional hernia are anticipated complications to abdominal surgery. Wound dehiscence is when the sutures in the abdominal wall separate, bursting the wound under the skin. Wound dehiscence is always a severe condition, especially in elderly and critically ill patients. Wound dehiscence can cause injury to intestines, as well as infection and organ failure. In cases where the sutures in the skin also fail, abdominal content can poke out through the skin. This is called burst abdomen. Normally patients that are affected by wound dehiscence need renewed surgery where the abdomen is resutured. Sometimes, because of swelling of the abdominal organs and infection, it is not possible to close the abdomen when wound dehiscence has occurred. In these cases, the abdomen must be left open and the patient will require repeated operations and intensive care before getting well. Wound dehiscence patients have a higher postoperative mortality rate than surgery patients in general, and there is also a high risk for incisional hernia after wound dehiscence.

Incisional hernia on the other hand develops when the wound has healed, but due to impaired healing of the abdominal tendon small bits of the peritoneum bulge under the skin, sometimes containing intra-abdominal fat. An incisional hernia can be very disabling, causing pain and local symptoms. In unlucky cases a sling of the small bowel can be caught in the incisional hernia. This is called incarceration and is a potentially life-threatening condition. Symptomatic incisional hernias normally need surgery. After an operation for incisional hernia patients may suffer from stiffness and pain from the abdominal wall. Yearly about 1800 incisional hernia surgeries are performed in Sweden according to the Swedish ventral hernia registry. A reduction of incisional hernias would save considerable health care resources and reduce suffering.

In recent years the methods to close the abdominal wall have developed, and studies show that a meticulous suturing technique for closing the abdominal wall can reduce the above-mentioned complications significantly. The new technique uses a suture that is slowly absorbed by the body. With this technique stitches in the abdominal tendon are made small and placed close together. The wound and the length of the suture is measured, and a quota is calculated to ensure that the right technique has been used.

Even after the new suturing technique has been introduced 5-10% of patients still develop an incisional hernia and a few percent a wound dehiscence. To further reduce these numbers, high risk patients must be identified, and special precautions made to protect them.

Many hospitals use the new technique for closing the abdominal wall, but far from all do. The department of Surgery at Capio S:t Görans hospital introduced the technique as early as 2012 in a structured quality effort, and the technique is integrated in standard practice and used by all abdominal surgeons.

The aim of this thesis has been to follow up on the structured implementation of the new surgical technique to see the long-term results.

By looking at large Swedish patient registries, this thesis has intended to identify risk factors for wound dehiscence and incisional hernia in the population.

Furthermore, to test a new technique to reinforce the abdominal closure to avoid wound dehiscence and incisional hernia.

Paper 1 – A retrospective study of the implementation of the new surgical technique at Capio S:t Görans hospital.

The study investigates the long-term impact of the change in technique by examining data on patients operated on before the implementation of the technique in 2012 and some years after the implementation.

93% of patients in the post implementation group had their abdomen closed according to the new technique, and the suturing technique was also correctly noted in the medical records. This compared to only 1% in the pre-implementation group. Incisional hernia and wound dehiscence proved to be at the same levels both before and after the implementation of the new technique, about 4-5%, which is normally considered an acceptable level. High BMI and postoperative wound infection proved to be risk factors for incisional hernia development. Male gender, high age, chronic obstructive pulmonary disease and wound infection were risk factors for wound dehiscence development.

Four years after the implementation, the new technique was fully integrated as standard practice at S:t Görans Hospital. The reason that there was no difference in complications between the groups is most likely due to that a sufficient surgical technique was already in use before the structured implementation.

Paper 2 – A study of the Swedish colorectal cancer registry to find the incidence of incisional hernia in the Swedish population.

This paper studies the incidence of incisional hernia in the Swedish population and looks for relevant risk factors by building a database combining the Swedish colorectal cancer registry and the Swedish national patient registry. The risk for developing an incisional hernia in the population was 5,3% for the population as a whole. Male gender, long surgery duration, age less than 70 years old, high BMI and wound infection were risk factors for incisional hernia development.

Paper 3 - A study of the Swedish colorectal cancer registry to find the incidence of wound dehiscence in the Swedish population.

By looking at the same database as paper 2, the incidence of wound dehiscence and relevant risk factors can be explored. A significantly higher risk for postoperative death is recorded for wound dehiscence patients. High age, male gender, high BMI, chronic obstructive pulmonary disease, systemic inflammatory disease, and a short surgery duration were risk factors for wound dehiscence in the study.

Paper 4 – Pilot study to test a new surgical devise.

In this study we tested a new technique where the abdominal wall, after suturing, is reinforced with a surgical net. The net that was tested is made from a synthetic material that is absorbed by the body in about 6 months. In this pilot study we found that the technique works and that there were no serious adverse events recorded.

Conclusions

Wound dehiscence and incisional hernia are dangerous and resource consuming complications to abdominal surgery.

High age, high BMI, long operation time, chronic obstructive pulmonary disease, and systematic inflammatory disease are risk factors for complication after abdominal surgery. There is also an increased risk for men.

Postoperative wound infection is a strong risk factor for further wound complications, and all possible actions should be undertaken to avoid wound infection.

A structured implementation when introducing a new surgical technique works well and has a long-lasting effect.

Implantation of TIGR® Matrix surgical mesh is a possible way to reinforce the abdominal wall after surgery.

POPULÄRVETENSKAPLIG SAMMANFATTNING

Stor bukkirurgi innebär dessvärre att komplikationer kan uppstå. Sårruptur och ärrbråck är två fruktade sådana komplikationer. En sårruptur innebär att suturerna i bukväggen släppt och att såret under huden spricker upp. En sårruptur är alltid ett allvarligt tillstånd, framför allt hos äldre, och kan leda till tarmskador, infektioner och organsvikt. Det kan också vara associerat med att hudsuturerna spricker upp, vilket i sin tur kan få till följd att bukinnehållet glider ut ur buken. Vanligen behöver patienter som drabbas av sårruptur en omoperation där buken sys ihop igen. Det händer att man pga. svullna tarmar och inflammation inte kan stänga buken efter en sårruptur. Då behöver buken lämnas öppen och det krävs intensivvård och upprepade operationer innan patienten är färdigbehandlad. Efter en operation av sårruptur är risken att senare utveckla ärrbråck mycket hög.

Till skillnad från sårrupturer innebär ärrbråck att operationssåret har läkt, men på grund av en defekt läkning av bukväggssenan buktar en mindre eller större snip av bukhinna och bukinnehåll fram under huden. Ett ärrbråck kan vara mycket invalidiserande och ge uttalade lokala besvär. I olyckliga fall kan en tarmslynga glida ut i ärrbråcket och klämmas fast. Detta kallas inklämning och är ett potentiellt livshotande tillstånd. Om patienten har uttalade besvär så behöver detta opereras. En operation av ärrbråck kan ge smärtor och stelhet i bukväggen. Årligen utförs c:a 1800 sådana operationer enligt svenska bukväggsbråckregistret. En minskning av antalet ärrbråck skulle spara stora sjukvårdsresurser och minskat lidande.

De senaste tio åren har metoden att försluta buken efter operation utvecklats och studier har visat att komplikationer enligt ovan kan minskas med en strukturerad och noggrann bukförslutningsteknik. Tekniken går ut på att man använder en tråd som långsamt löses upp av kroppen efter c:a sex månader och att man syr med små täta tag i bukväggssenan. Sedan mäter trådåtgång och sårets längd och räknar ut en kvot för att kontrollera att rätt teknik har använts.

Även med modern sutureringsteknik drabbas c:a 5-10% av patienterna av ärrbråck och några procent av sårruptur. För att ytterligare minska dessa risker behöver högriskpatienter kunna identifieras och ytterligare åtgärder vidtas för att skydda dessa.

Många sjukhus, inte bara i Svergie, använder idag en strukturerad teknik för bukförslutningen, men långt ifrån alla gör det. Kirurgkliniken vid Capio S:t Görans sjukhus introducerade tidigt den nya tekniken och började redan 2012 att försluta buken enligt ett standardiserat vetenskapsbaserat protokoll som sedan dess följs av alla klinikens kirurger.

Syftet med detta avhandlingsarbete har varit att följa upp hur införandet av en standardiserad bukförslutningsteknik fungerat på Capio S:t Ggörans sjukhus och hur resultaten på lång sikt påverkats.

Genom att använda de stora svenska patientregistren identifiera riskfaktorer för ärrbråck och sårruptur i den svenska befolkningen.

Testa en ny teknik för att förstärka bukförslutningen så att inte sårruptur och ärrbråck uppstår.

Arbete 1 – En återblick på införandet av den strukturerade bukförslutningstekniken vid Capio S:t Görans sjukhus

Vi undersökte vad bytet till den moderna strukturerade bukförslutningstekniken hade för effekt på lång sikt. Genom att samla in data på patienter opererade innan införandet 2012 och data frånpatienter som opererats fyra år efter införandet samlade vi totalt 1120 patienter. Vi fann att 93% av patienterna i den sena gruppen hade fått buken försluten med en korrekt teknik, vilket också noterats korrekt i journalen, att jämföras med 1% före införandet. Ärrbråck och sårruptur visade sig vara lika vanligt före som efter införandet av den nya tekniken, c: a 4–5%, vilket anses vara en acceptabel nivå. Högt BMI och postoperativ sårinfektion visade sig vara riskfaktorer för att utveckla ärrbråck. Manligt kön, hög ålder, kronisk obstruktiv lungsjukdom samt sårinfektion var riskfaktorer för sårruptur.

Fyra år efter införandet var den nya tekniken helt integrerad i vårt arbetssätt. Att skillnaden inte var så stor beror sannolikt på att de flesta kirurger använde en tillräckligt bra teknik redan före införandet av den strukturerade tekniken.

Arbete 2 – Studie på det svenska Colorektalcancerregistret för att få en bild av ärrbråcks utbredning hos patienter opererade för Colorektalcancer.

I den här studien tittade vi på förekomsten av ärrbråck och sökte efter riskfaktorer för ärrbråcksutveckling genom att bygga en databas där vi kombinerade data från det svenska Colorektalcancerregistret och Slutenvårdsregistret. Risken att utveckla ärrbråck I studiepopulationen var 5,3%. Manligt kön, lång operationstid och ålder under 70 år, högt BMI och sårinfektion visade sig vara signifikanta riskfaktorer för ärrbråcksutveckling

Arbete 3 -– Studie på det svenska Colorektalcancerregistret för att få en bild av sårrupturers utbredning.

Genom att titta i samma databas som i arbete 2 kunde vi utvärdera förekomsten av sårruptur efter Colorektalcancerkirurgi och dess riskfaktorer. Det var en signifikant ökad risk att dö i inom 30 dagar från operationen för de patienter som utvecklade sårruptur. Hög ålder, manligt kön, högt BMI, Kronisk obstruktiv lungsjukdom, systemisk inflammatorisk sjukdom och kort operationstid visade sig vara riskfaktorer.

Arbete 4 – Pilotstudie för att testa nytt nätmaterial.

I det här arbetet testade vi en ny teknik där man förstärker bukförslutningen med ett nät. Nätet som vi testade var av ett resorberbart material som tas upp av kroppen och med tiden försvinner. I den här pilotstudien fann vi att tekniken fungerade och att inga allvarliga komplikationer inträffade.

Slutsatser

Ärrbråck och sårruptur är farliga och kostsamma komplikationer till bukkirurgi.

Hög ålder, högt BMI, lång operationstid, kronisk obstruktiv lungsjukdom, systemisk inflammatorisk sjukdom är riskfaktorer för komplikation efter öppen bukkirurgi. Det föreligger också en ökad risk för män.

Infektion i operationssåret är en stark riskfaktor för ytterligare komplikationer och man bör vidta alla åtgärder för att undvika infektion.

Strukturerat införande av en ny kirurgisk teknik fungerar och har en bestående effekt.

Implantation av ett TIGR® Matrix nät är ett möjligt sätt att förstärka bukväggen efter kirurgi.

ABSTRACT

Background

Incisional hernia and Wound dehiscence are potentially serious complications to midline incisions. Recent studies have shown that a meticulous suturing technique can reduce the rate of these complications significantly, but even with optimal technique there is 5-15% risk of abdominal wall complications. At Capio S:t Görans hospital the new abdominal wall closure technique 2012 was implemented in a standardised quality improvement project.

The aim of these studies was to investigate the effect of a structured implementation of the new surgical technique, to study which risk factors for incisional hernia and wound dehiscence are relevant in a Swedish population and to test new techniques to reinforce the abdominal wall after open abdominal surgery.

Methods

Study 1.
All procedures performed via a midline incision 2010-2011 before, and 2016-2017 after the new protocol was introduced at Capio S:t Görans Hospital were identified and assessed for complications and risk factors for wound dehiscence and incisional hernias

Study 2.
All procedures registered in the Swedish Colorectal Cancer Register (SCRCR) 2007–2013 were identified. Patients with comorbid disease diagnoses, registered at admissions and visits prior to the procedure and relevant to this study, were obtained from the National Patient Register (NPR). Data on occurrence of incisional hernias were obtained by combining data from the SCRCR and the NPR).

Study 3.
Like study 2 all open abdominal procedures for colorectal cancer registered in the SCRCR 2007–2013 were identified. Potential risk factors for wound dehiscence were identified by cross-matching between the SCRCR and the NPR. The endpoint in this study was reoperation for wound dehiscence registered in either the SCRCR or NPR.

Study 4
Sixteen patients with three or more risk factors for wound dehiscence or incisional hernia were included. A TIGR® Matrix mesh was placed on the aponeurosis with an overlap of five cm on either side and fixated with continuous monofilament polydioxanone suture. All postoperative complications were registered at clinical follow-up.

Results

Study 1

After the implementation of new guidelines, 93% of procedures were performed using the standardised technique for abdominal wall closure. There was no significant difference in incidence of incisional hernia or wound dehiscence between the two periods. BMI>25 and postoperative wound infection were found to be independent risk factors for incisional hernia. Male sex, high age, chronic obstructive pulmonary disease, and postoperative wound infection were risk factors for wound dehiscence.

Study 2

The cumulative incidence of incisional hernia in the population was 5.3%. In multivariate analysis male gender, operation time exceeding 180 min, body mass index (BMI) > 30, age < 70 years and postoperative wound complication were significant risk factors for incisional hernia.

Study 3

In multivariable analysis, age > 70 years, male gender, BMI

> 30, chronic obstructive pulmonary disease, generalised inflammatory disease, and duration of surgery less than 180 min were significant risk factors for wound dehiscence. The hazard ratio for postoperative

death was 1.24 for patients who underwent reoperation for wound dehiscence compared with that for controls.

Study 4

One patient developed a seroma that needed drainage and antibiotic treatment. One patient had a wound infection that needed antibiotic treatment. There was no complication requiring a reoperation. No wound dehiscence or incisional hernia was seen.

Conclusions

High age, high BMI, long operation time, chronic obstructive pulmonary disease, systemic inflammatory disease, and male gender should be considered risk factors for postoperative adverse events after a midline incision.

Postoperative wound infection is a strong predictor of incisional hernia and wound dehiscence and all measures possible should be taken to avoid wound infection.

Structured implementation of a standardised surgical technique is possible and has a long-lasting effect.

Implantation of TIGR® Matrix mesh is a feasible way to reinforce the abdominal wall after high-risk surgery.

LIST OF SCIENTIFIC PAPERS

I. Small Stitch Small Bites technique: a long-term follow-up.
Submitted

II. Incisional hernia after surgery for colorectal cancer: a population-based register study.
Int J Colorectal Dis. 2019 Oct;34(10):1757-1762

III. Incidence of wound dehiscence after colorectal cancer surgery: results from a national population-based register for colorectal cancer.
Int J Colorectal Dis. 2018 Oct;33(10):1411-1417

IV. Prophylactic Resorbable Synthetic Mesh to Prevent Wound Dehiscence and Incisional Hernia in High High-risk Laparotomy: A Pilot Study of Using TIGR Matrix Mesh
Front Surg. 2016 May 18;3:28

LIST OF ABBREVIATIONS

SSSB	Small Stitch Small Bites Technique for closing the abdominal wall
RCT	Randomized controlled trial
NPWT	Negative pressure wound therapy
COPD	Chronic obstructive pulmonary disease
PRF	Perirenal fat surface area
BMI	Body mass index
IR	Insulin resistance
ERAS	Enhanced recovery after surgery
MMP	Matrix metalloproteinase
ASA	American society of anesthesiologist's physical status classification
SCRCR	Swedish colorectal cancer registry
NPR	Swedish national patient registry
PDS	Polydioxanone suture material
ICD	International classification of disease
SSI	Surgical site infection
HIPEC	Hyperthermic intraperitoneal chemotherapy
CT	Computed tomography

CONTENTS

1 BACKGROUND

1.1 INTRODUCTION

In 2012 I became aware that the rate of wound dehiscence in our general surgery department was too high. I investigated the problem and found good evidence to suggest that we should implement a structured closure technique after midline incision of the abdominal wound, to reduce this complication. After discussions and education of the surgical staff, we implemented the Small-Stitch-Small-Bites technique (SSSB) in the summer of 2012 to improve the safety of abdominal wall closure. This had an immediate and dramatic impact on outcome. In the spring prior to implementation, twelve patients suffered a burst abdomen which needed acute reoperation and prolonged hospital stay. In the autumn that same year only one patient needed reoperation for a burst abdomen. I was amazed that such a simple intervention could have such an impact. In the years following implementation of SSSB the lower rate of wound dehiscence persisted with four-five cases per year. In my initial follow-up, I found that wound dehiscence patients needed a long hospital stay and that our intervention saved us more than one bed per day all year round in our ward. Furthermore, resources were saved due to a reduction in incisional hernia surgery. This experience led me to further investigate the mechanisms of wound dehiscence and incisional hernia, and to see if it is possible to reduce the risks associated with midline incisions. This thesis is the result of these studies.

The aim of this thesis has been to follow up on the structured implementation of the new surgical technique to see the long-term effect.

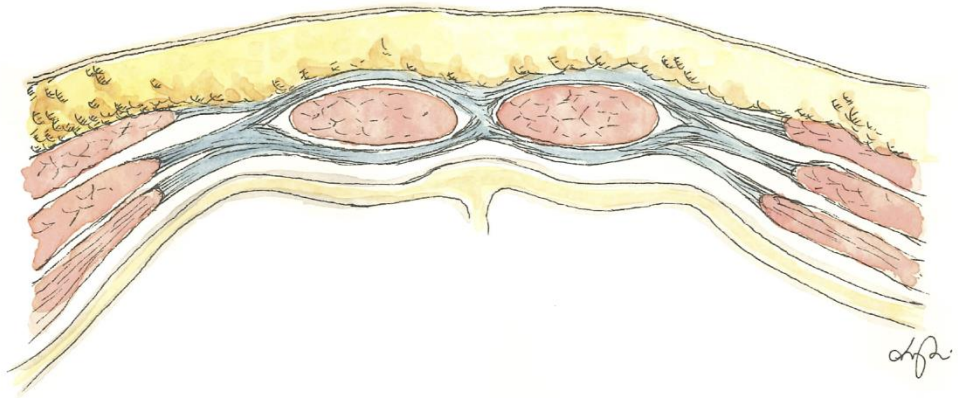
Studying the incidence of incisional hernia and Wound dehiscence after a midline incision.

Identifying risk factors for wound dehiscence and incisional hernia in the Swedish population.

Testing a new technique to reinforce the abdominal closure to avoid wound dehiscence and incisional hernia.

1.2 ANATOMY OF THE ABDOMINAL WALL
(1–3)

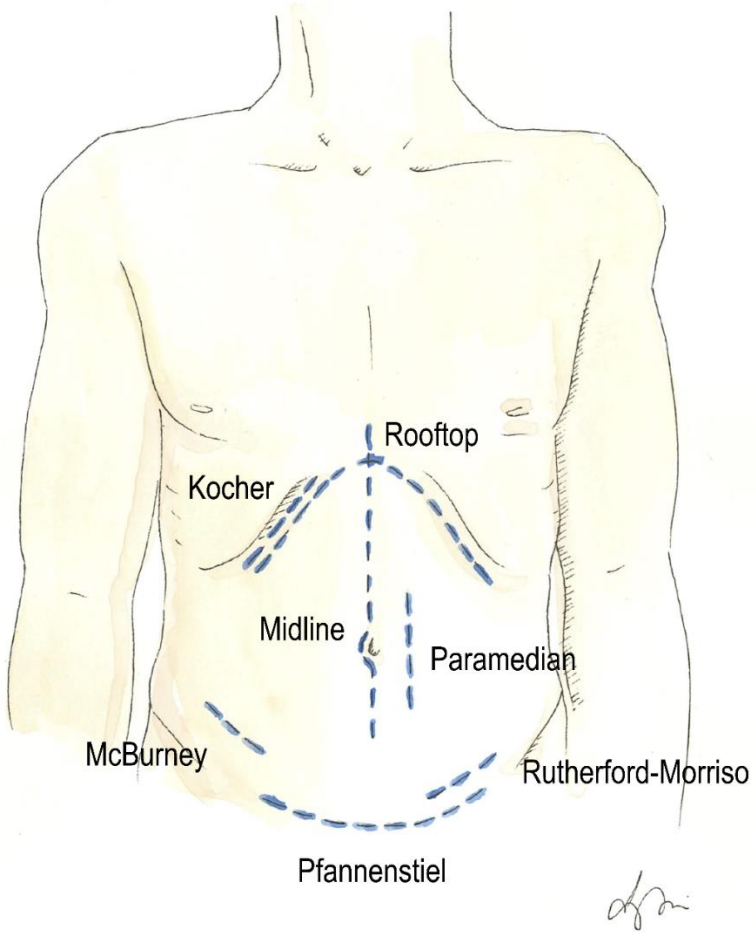
The abdominal wall is a complex construction of muscles, nerves, vessels, aponeuroses, and tendons bridging between the thorax and the pelvis. The functional purpose of the abdominal wall is to keep the trunk upright and support movement. The abdominal wall also protects the internal organs and keeps them in place. Defects in the abdominal wall can thus affect posture, impair mobility, and cause displacement of internal organs.
The lateral abdominal wall has three flat muscles. The transversus abdominis, as its name suggests, runs transversely and is the innermost muscle. The main function of the transversus abdominis is to hold the internal organs in place during activity. The internal oblique muscle runs laterocaudally from the midline. The internal oblique takes part in breathing and can turn and tilt the upper body. The external oblique muscle runs laterocranially from the midline. The main function of the external oblique is rotation and flexion of the upper body. These three flat muscles form the core construction of the abdominal wall that supports movement and posture, and confines and protects the internal organs. The rectus abdominis muscles run in craniocaudal direction on either side of the midline. The aponeuroses of the three flat muscles form the rectus sheath within which the rectus abdominis muscle runs. The recti abdominis are the main flexors of the upper body. The rectus sheaths meet in the midline where they join to form the linea alba, also named the rectus aponeurosis. The blood supply to the abdominal wall comes from two systems. The epigastric arteries run in a craniocaudal direction parallel to the midline on both sides. The intercostal and subcostal arteries as well as the circumflex iliac arteries form branches that run between the transverse and the internal oblique muscles. The nerve supply to the abdominal wall muscles is derived from the lower intercostal nerves, the thoracoabdominal nerves and the iliohypogastric nerves. The rectus aponeurosis is a strong tendinous, avascular structure with little nerve supply.



Anatomy of the abdominal wall © Lucy Bai 2021

1.3 THE MIDLINE INCISION

Throughout surgical history a variety of incisions have been used to access the abdominal organs, all having advantages and disadvantages (4). The midline incision is associated with low risk for damage to nerves or vessels (1,5). Furthermore, it does not require transection of muscles, which makes it fast and easy to perform (3,6,7). The level of the midline incision may be chosen depending on what procedure is intended, and it is easy to extend the incision if necessary. The midline incision provides good access to most abdominal organs and is suitable for acute surgery. A disadvantage of the midline incision is the relatively high risk for incisional hernia (6–11).



Abdominal Incisions © Lucy Bai 2021

1.4 PRINCIPLES OF WOUND HEALING

Wound healing after an incision can be divided into three phases (9,12,13). During the first acute inflammatory phase, vasodilatation leads to an invasion of leucocytes and macrophages. The main role of these cells is to remove dead cells and debris from the incision site and to protect the wound from bacterial invasion. The macrophages also attract fibroblasts, which are important in the early phase of regeneration (9,12,13). The extent of the acute inflammatory reaction ranges from 0.5 cm to 1.5 cm from the fascial edges, somewhat wider if wound infection is present (9,12,14,15). During the acute inflammatory phase, which lasts for about four days, the wound itself has no tensile strength. During this period the suture holds the entire tensile strength of the wound which explains why wound dehiscence most often occur during this phase (14,16,17). Infection during the acute inflammatory phase increases the number of leukocytes but not macrophages. This prolongs the acute inflammatory phase, but the decline in macrophages decreases the number of fibroblasts attracted (12). There is evidence that the use of diathermy, especially in the coagulation mode, can affect the blood supply of the fascial edges and inhibit wound healing (18).

The second, regenerative phase, is characterised by collagen formation mediated by invading fibroblasts (9,12). Disturbances in collagen metabolism is believed to play a major role in the formation of incisional hernia (12,17,19–22). There are over twenty collagen types, all with individual characteristics. Collagen type I gives strength to the scar whereas the role of collagen type III is primarily to form a matrix. Collagen type III is produced in the early remodeling phase. The weaker collagen type III is then remodeled to collagen type I. The collagen type I/III ratio is used as a measure of collagen quality (19,21). A lower collagen I/III ratio is seen in incisional hernia patients than in controls (19,22). The collagen I/III ratio can be measured in skin, fascia, or in rectus aponeurosis tissue itself to identify patients with a high risk for incisional hernia (19,21,22). Another way to identify patients at risk is to measure the turnover of different types of collagen. Reduced turnover of collagen type V (Matrix) and increased turnover of collagen type IV (strength) is seen in patients who develop an incisional hernia. (23) Matrix metalloproteinases (MMP) break down extracellular matrix and may serve as markers of collagen turnover. Levels of certain MMPs are believed to predict hernia formation (17,19,21). MMP-2 activity is increased in obese patients, resulting in an increased breakdown of type I collagen during the regenerative phase. This leads to a reduced type I/type III collagen ratio, and thus the synthesis of mechanically weaker tissue (24). Abdominal aortic aneurysm is significantly associated with hernia formation and shares many risk factors. MMP-2, MMP-9 and MMP-13 activities are associated with both hernia and aneurysm disease, indicating that both could be symptoms of a systematic connective tissue disease (22,25,26).

The regenerative phase lasts for approximately three weeks. At the end of the regenerative phase the wound has achieved 15-20% of the original tissue's strength (2,9,12).

The third remodeling phase lasts up to one year. During this phase, mechanical tension of the wound stimulates collagen remodeling leading to more organized and stronger structures. By

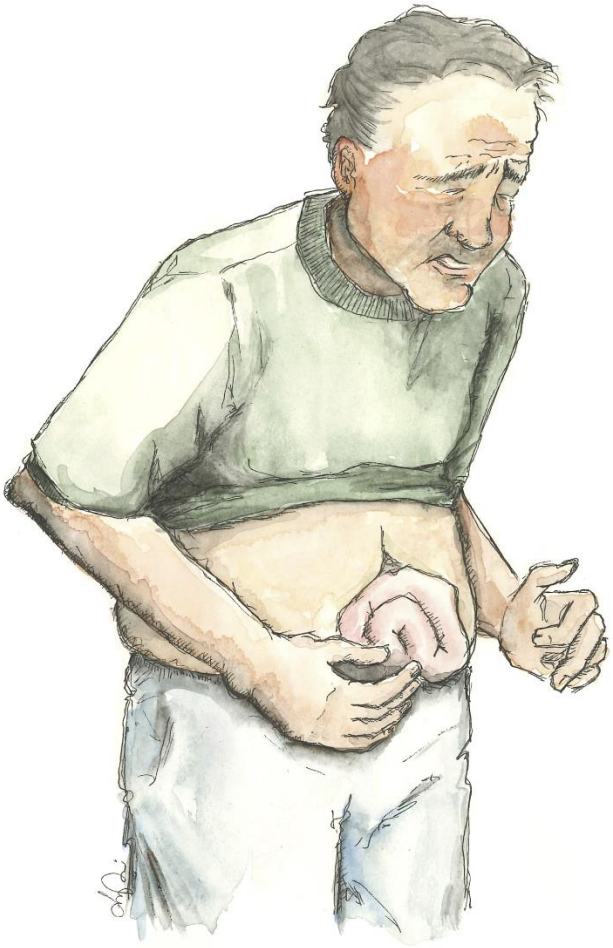
the end of this phase, the rectus aponeurosis has regained 60-90% of its original strength (9,12,13).

1.5 INCISIONAL HERNIA

Incisional hernia is defined as any abdominal wall gap with or without a bulge in the area of a postoperative scar perceptible or palpable by clinical examination or imaging (27). Simply put, an incisional hernia is a defect in the abdominal wall covered by neoperitoneum, formed at the site of a previous surgical incision. Sometimes the hernia is just a defect, and sometimes a lump is formed under the scar. The hernia sac can contain abdominal fat or organs and in unfavourable cases this can lead to incarceration and strangulation of the hernia sac contents. The rate of incisional hernia after open abdominal surgery varies in the literature. It is normally reported to be up to 20% (28,29), but in more recent studies it has been shown to be as low as 5-13% with meticulous suturing technique (30,31). An incisional hernia can present years after index surgery (32–34). The late diagnosis of incisional hernia can partly be due to authors using different definitions of incisional hernia. With the definition above, about 90% of hernias can be detected within a year after index surgery (6). In most cases, incisional hernias can be diagnosed by thorough clinical examination, but complementation with computed tomography can be helpful in obese patients (32,35). In a study by Ah-Kee et al, one third of patients were not aware they had an incisional hernia, and one third had noticed the defect but were asymptomatic (29). Typical symptoms of incisional hernia include pain, discomfort, functional disability, and cosmetic disturbance (29,36). The natural course of incisional hernia is not known, nor the probability of an asymptomatic patient developing symptoms. Reports in the literature state that only 1% of hernia patients suffer incarceration (36). In a systematic review by Bosanquet et al 2015 (37), the overall cumulative incidence of incisional hernia was 12%. Forty-nine per cent of patients with an incisional hernia were symptomatic and 36% underwent surgery. Incisional hernia is costly (38,39) and prevention of may thus be considered a very cost-effective measure (39,40). In the USA, the number of operations for incisional hernia and the cost of each operation increased each year between 2007 and 2011. One of the reasons for this is that we tend to operate on older patients with greater comorbidity (41).

1.6 ABDOMINAL WOUND DEHISCENCE

Wound dehiscence is defined as separation of the abdominal fascia after surgery (9) . There are four principal mechanisms of wound dehiscence: suture rupture, knot failure, slack suture (because of large bites including fatty tissue), or sutures cutting through the fascia; the last-named being the most common (14,42–44). Early wound dehiscence can be dramatic with protrusion of abdominal organs through the wound; also known as burst abdomen. More frequently, however, wound dehiscence is a subclinical condition that is seen as a precursor of incisional hernia (16,45,46). Of patients that have a radiologically diagnosed wound dehiscence at an early stage, 92% later develop an incisional hernia (46). Wound dehiscence usually occurs during the first 3-7 days (47–50) but diagnosis is often delayed. Burst abdomen is rare, with an incidence of approximately two per cent of elective abdominal surgery patients. In acute or emergency cases, the reported incidence of burst abdomen is as high as 12-50% (9,51,52). At clinical examination, early wound dehiscence presents with secretion from the wound, that is often misinterpreted as an infection. More severe cases can be easily diagnosed with CT-scan where dehiscence in the fascia is seen with abdominal organs close to the skin. Depending on the size of the fascial defect, there is a risk for ischaemia of protruding organs (9). Burst abdomen is a very serious condition with high morbidity and a reported mortality of 25% or higher (48,52–56), and hospital stay is significantly longer (44). In the case of a large fascial dehiscence, emergency surgery is needed. There are no large RCTs on the various treatment options for burst abdomen, and the evidence level is weak. If possible, an attempt is made to close the wound. However, due to intra-abdominal swelling, deep infection, or poor fascia quality, the wound is sometimes left open for a while before closure. Patients that are primarily sutured for burst abdomen have a very high incidence of incisional hernia (52,53,56–58). Closure and reconstruction with a mesh may provide a safer outcome and should be considered in these patients (52,59,60). The placement of a mesh does not seem to increase formation of enterocutaneous fistulae, (59) and seems safe even in a contaminated environment. For patients where primary closure is not possible, the recommendation is to use a dynamic closure technique where the fascial edges are kept under traction over a period until it is possible to close the wound. There are several different systems for dynamic wound closure, some of which can be used in combination with negative pressure wound therapy (NPWT) (60,61). A promising new concept for dynamic wound closure, where a combination of mesh augmentation and NPWT is used, has been described by Petersson et al (62). Patients that are operated for burst abdomen suffer a poor body image and low quality-of-life (57).



Wound dehiscence © Lucy Bai 2021

1.7 RISK FACTORS FOR WOUND DEHISCENCE AND INCISIONAL HERNIA.

Many studies have been performed to identify risk factors for incisional hernia and wound dehiscence (55,63–65) but only a few have been performed after new guidelines for closing the abdominal wall were published in 2014 (4,49). Most studies do not describe the surgical technique used to close the aponeurosis and thus neglect one of the most important risk factors (2). All the risk factors presented here were reported in studies performed before the closure paradigm shift, and may be considered irrelevant since studies performed after the 2014 guidelines fail to show any significant risk factors (66). When Millburn et al first reported the excellent outcome of the SSSB technique, they found no significant risk factors. In a retrospective study by Aksamija et al on over 3000 patients operated 2013-2016, 44 (1,25%) cases of clinically significant wound dehiscence were found; too few to find significant risk factors (49).

In 2018, Wiegering et al presented an interesting retrospective control-matched cohort study (67) where they could exactly specify which surgical technique had been used. The same technique was used in all patients (continuous monofilament, with a suture length /wound length ratio of over 4:1). In that study, no significant risk factors for incisional hernia could be found, and they failed to show that abdominal aortic aneurysm surgery patients have a higher risk than colon cancer patients for incisional hernia. This confirms the findings of Israelsson et al (68,69), that with a good suturing technique the disease behind surgery has little importance for the development or not of incisional hernia.

With meticulous suturing technique, prospective randomized trials predict a cumulative incidence of incisional hernia around 6-10% and burst abdomen approximately 1%. With such small incidences, large multicentre studies are required to further assess the underlying risk factors.

Wound dehiscence and incisional hernia represent two different conditions with the same pathogenesis (46), both having their origin in the early separation of the fascial edges. Table 1 shows known risk factors for incisional hernia and wound dehiscence and the studies that support them. Although surgical technique is the most important risk factor (31,66), we still need to be aware of the other risk factors. The presence of five or more of these risk factors has been suggested as a cut-off for high risk (65).

One systematic review by Bosanquet et al 2015, including data from 14 618 patients, found that age, previous midline incision, previous hernia, AAA-surgery, surgery for obesity, and upper abdominal surgery were all risk factors (37).

Several attempts have been made to design a risk score for incisional hernia and wound dehiscence.

Ramshorst et al, in a large retrospective case-control study including patients between 1985 and 2005, assessed risk factors for wound dehiscence and developed a risk score model (64). Their aim was interesting, but the risk score they developed is limited by the fact that it

includes two strong postoperative risk factors, wound infection and postoperative coughing. These two risk factors have an overwhelming influence on the risk for abdominal wall complications but are impossible to use as targets for prevention, making the model unsuitable to identify patients that require pre- or perioperative prophylactic measures.

Goodenough et al, in a study based on open vs laparoscopic surgery taking into account a variety of methods for closing the abdominal aponeurosis, prospectively assessed risk factors for incisional hernia and suggested a risk score (70). They found that apart from open surgery, obesity and COPD were significant risk factors.

The most recent risk calculator comes from the University of Pennsylvania. In a retrospective study, Basta et al collected information from over 29 000 patients from large databases and developed a risk score based on preoperatively known risk factors for incisional hernia (71). The material for this study was wide and included gynaecologic and urologic surgery, as well as open and laparoscopic approaches. The overall rate of incisional hernia in the study was 3.8%. Risk factors included colorectal surgery, history of previous abdominal surgery, and smoking. No information on the method used for closing the abdominal wall was given. The risk predictor is easily available as a smartphone app or online (72).

These risk models are useful tools for preoperative workup to identify patients at high risk for incisional hernia. As yet, no risk model exists that assumes use of the small-stitch-small-bites surgical technique, and there is a need for more studies to identify risk factors that remain relevant using this modern surgical technique.

Itatsu et al, 2014, published a large well-designed study including over 4000 patients (73). They concluded that high BMI, thick subcutaneous fat, age, chemotherapy, female sex, and blood transfusion were independent risk factors. Although the authors state that a continuous slowly absorbable monofilament suture should be standard for closure, only 443 of the 4000 patients had the aponeurosis closed with this technique. In the risk analysis, there was an increased risk for incisional hernia when using interrupted sutures, but this was not significant.

Wound infection is a very strong risk factor for both incisional hernia and wound dehiscence (64,65,69,74,75). Wound infection is a postoperative outcome with its own risk factors (76,77). To lower the rate of incisional hernia and wound dehiscence risk factors for wound infection can be assessed preoperatively in the risk score. One theory is that some cases reported as a wound infection might, in fact, be early wound dehiscence. This theory has yet to be confirmed, although Millbourn et al concluded that compared to closure with small stitches, the use of large stitches doubled the risk for wound infection and that is an independent risk factor (77). This suggests that wound infection in some cases is caused by early wound dehiscence, not the opposite, but more studies are needed to examine this.

Obesity (BMI>30) (65,70,73,75,77–81) and male gender (64,75,77,82) are frequently reported risk factors for incisional hernia and wound dehiscence. In a retrospective study, Aquina et al found that visceral obesity, not high BMI per se, should be regarded as a risk factor for incisional hernia (83). Visceral obesity is easily approximated by measuring the perirenal fat surface area (PRF). Studies confirm that a high PRF predisposes to postoperative complications (84–86). Another suggested measurement is the Hip-Waist Ratio which has been shown to be a better predictor of complications after surgery than BMI (87). Male sex predisposes to visceral obesity (88), and this possibly explains some of the gender difference.

One underlying factor associated with obesity and postoperative complications is insulin resistance (IR). Insulin resistance is common after major surgery, even in non-diabetic patients (89), and animal studies show that IR leads to impaired wound healing after surgery (90). Obesity has a strong association with IR and about 40% of obese patients can be expected to be insulin resistant (91,92). This association is also evident for visceral obesity (93). Perioperative IR can be prevented by carbohydrate loading (94), and because of its association with postoperative complications, IR is targeted and treated in the enhanced recovery after surgery (ERAS) programme (95).

The role of connective tissue quality in the development of incisional hernia is a topic of great interest. As explained in the section on hernia formation, the turnover of collagen type V (matrix) is reduced, and the turnover of collagen type IV (strength) is elevated in hernia patients. Biomarkers of collagen type IV turnover are altered in hernia patients (17) as is the collagen I/III ratio (19). Pogacnik et al, 2014, examined the risk for incisional hernia in colon cancer patients and diverticulitis patients undergoing sigmoid colectomy. They found an increased risk for incisional hernia in the diverticulitis group. This suggests that diverticulitis patients have impaired connective tissue function that predisposes to their disease as well as to incisional hernia (78). Future studies on incisional hernia should recognize connective tissue quality and collagen metabolism as potential risk factors. Smoking is a strong independent risk factor for fascial dehiscence (82,96) and this should also be included in future studies.

1.7.1 Table 1 Reported risk factors for wound complication

Significant risk factors	Ref nr
High age	(37,55,64,65,69,73,81,82)
Emergency surgery	(55,64)
Cancer	(11,55,65,81)
Haemodynamic instability	(55,65,73,78)
Male gender	(64,75,77,82)
Female gender	(73,88)
Hypertension	(64,65)
Chronic pulmonary disease	(64,65,70,75,81)
Ascites	(64,65)
Anaemia	(11,64,81)
Jaundice	(64)
Corticosteroid use	(64,65,78,81,89)
Sepsis	(64,65,81)
Postoperative coughing	(63,64)
Wound infection	(63–65,68,69,74,75,77)
Obesity	(11,65,68,70,73,75,77–81,88)
Ostomy	(65,78)
Hypoproteinaemia	(65,88)
Uraemia	(65)
Left colon or rectal cancer	(88)
Chemoterapy	(73,81,90)
Previous hernia	(37,78,90,91)
Thick subcutaneous fat	(73)
High ASA score	(78)
Abdominal aortic aneurysm repair	(37,80)
Smoking	(11,81,82)
Diabetes	(81)
Radiotherapy	(81)

1.8 THE SMALL-STITCH-SMALL-BITES (SSSB) TECHNIQUE

There has been a paradigm shift on midline incision closure over the past ten years based on the findings of the Sundsvall group (30,30,40,42,66,68,68,77,97,98). The Sundsvall results have also been reproduced in the STITCH trial (31). This method has become the recommended standard since 2014 (4,28,99) and has seen widespread use since 2010.

The work that made way for the modern technique for abdominal wall closure began in 1976 when Jenkins suggested that a running monofilament suture with a suture length to wound length ratio of at least 4:1 would prevent suture cutting through the tissue, thereby avoiding burst abdomen (100). In 1994, Israelsson et al showed that a slowly absorbable suture was as safe as nylon when closing the abdominal wall (101). Sahlin et al conducted a randomised controlled trial that failed to show that the continuous suture is superior to the interrupted technique, though the continuous suture was as good as the interrupted (102). In 1995, Niggebrugge et al showed that a running monofilament suture was superior to the interrupted technique to prevent incisional hernia (74).

Jenkins ideas were taken up by Israelsson et al in1993 when they proved that a suture length to wound length ratio greater than 4:1 reduces the rate of incisional hernia (69). They also found that the 4:1 method reduced midline incision complications (68,103), and that the technique was cost effective (39).

In animal studies, Cengiz et al 2001 showed that only including the aponeurosis in the sutures instead of mass layer suture leads to less fascial separation (98), and that small tissue bites with a suture length /wound length ratio of at least 4:1 gives higher bursting strength than large bites (97). This was confirmed by Harlaar et al in 2009 showing that small stitch length and small distance between the stitches gives the suture line better tensile strength than large stitches (104). Millbourn et al, 2004, re-evaluated old data from the Sundsvall group, concluding that short stitch length (small bites) is preferable. (30)

In a randomised controlled trial Millbourn et al tested the SSSB method. They showed that closing the abdominal wall with a running suture and a suture length to wound length ratio of at least 4:1 with small bites involving only the aponeurosis is superior to large (at least 10mm) bites in preventing wound dehiscence and incisional hernia (66,77). The rate of incisional hernia using the small bites method was 5,6% compared to 18% in the large bites group (77). In 2015, Deerenberg et al published their randomised controlled trial comparing small bites to large bites, where small bites gave an incisional hernia rate of 13% and large bites 21% (31).

In 2014, the European Hernia Society recommended “a slowly absorbable monofilament suture in a single layer aponeurotic closure technique without separate closure of the peritoneum, and that the small bites technique with a suture to wound length (SL/WL) ratio at least 4/1” (4) should be used to prevent wound dehiscence and incisional hernia formation.

Recording suture length to wound length ratio in the surgical report is a routine that does much to ensure that the appropriate technique is being applied (69,75). In 2014, Walming et al attempted to confirm this in a retrospective study (75) but they failed to do so, probably because a meticulous suturing technique was already standard even though the ratio was not noted in the report. This highlights the need for a universal way to describe the technique used for abdominal wall closure to be able to review outcomes retrospectively.

1.9 PROPHYLACTIC MESH AUGMENTATION

Despite meticulous suturing technique, approximately 5-10% of patients develop an incisional hernia and 1% suffer burst abdomen. The use of prophylactic mesh augmentation has been suggested to prevent these adverse events (4,105). In a meta-analysis from 2013, Bhangu et al concluded that prophylactic mesh applied as onlay, inlay, or sublay, significantly reduces the risk for incisional hernia in high risk patients (105).

In 2017, Borab et al concluded that prophylactic mesh dramatically reduces the risk for incisional hernia, but at the cost of more seroma formation and the possibility of chronic pain (106). Studies included in their review used both sublay and onlay placement. The increase in risk for seroma formation was mostly seen in the onlay mesh population.

Caro-Tarrago et al, in a randomised controlled trial, found that onlay mesh reduces the rate of incisional hernia. They also pointed out that although onlay mesh leads to more seroma formation, all their patients could be managed conservatively (107). The onlay technique is easily learned and fast compared to the sublay technique (107). This makes onlay placed mesh a suitable prophylactic measure.

At present there is no consensus as to which patients require mesh, what material should be used, and in which position the mesh should be placed (4). More studies on these issues are needed.

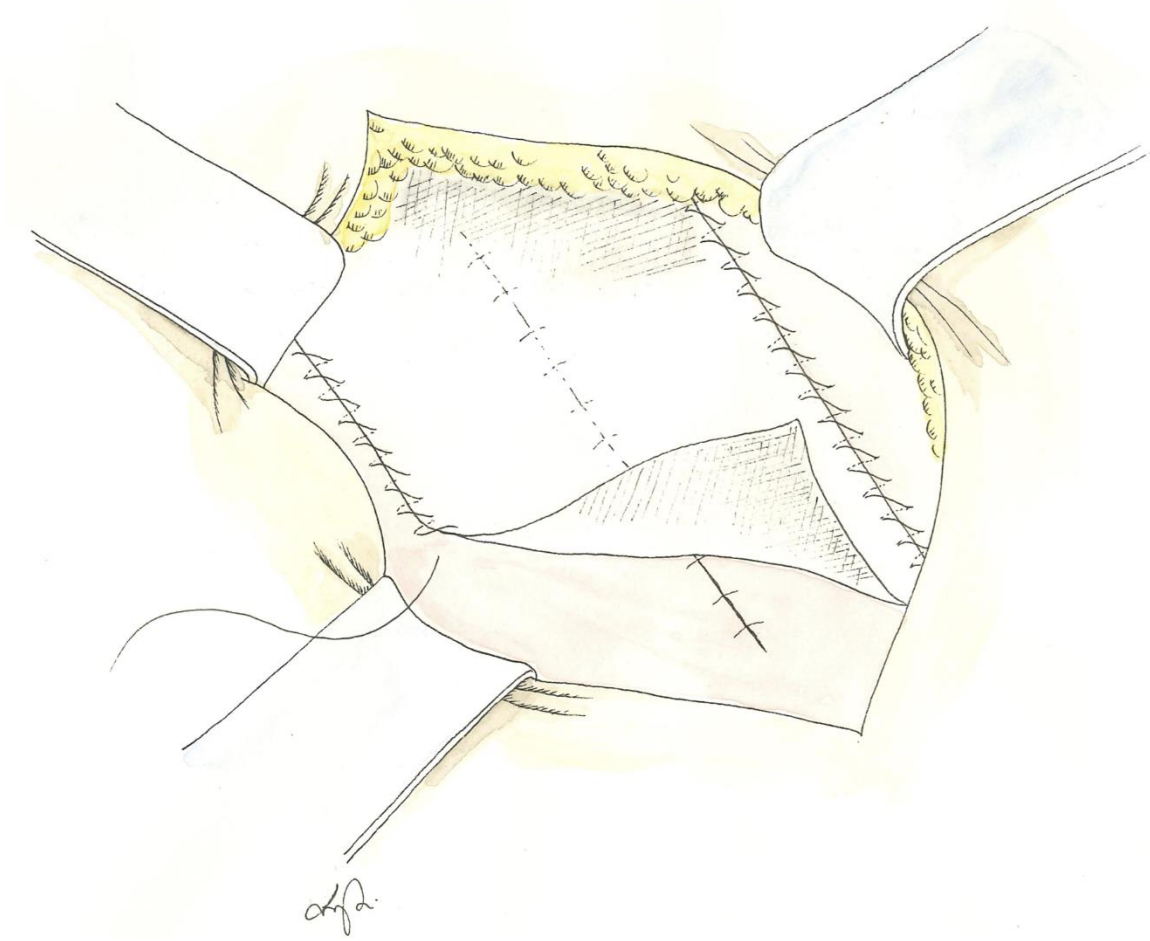
1.10 PROPHYLACTIC RETENTION SUTURES

Another technique to reduce the rates of incisional hernia and burst abdomen is to reinforce a tensioned suture line using retention sutures. Retention sutures are strong and are placed at wide intervals across the incision line deep within the musculature and fasciae of the abdominal wall. A skin protection device is often used, and the retention sutures are left for some days to lessen the tension on the midline incision during the initial healing phase. Retention sutures are easily removed by cutting the suture at the skin and then withdrawing them. In 2013, Khorgami et al suggested that retention sutures could prevent wound dehiscence in a high risk population (108). Modern closure techniques were not used in their study and they reported a 13% clinically significant wound dehiscence rate in the control group. The European Hernia Society reviewed the evidence for retention sutures and concluded that they should not be recommended in their guidelines (4). More studies are required to support the use of retention sutures.

1.11 SWEDISH COLORECTAL CANCER REGISTRY AND THE NATIONAL PATIENT REGISTRY.

The Swedish Colorectal Cancer Register (SCRCR) is a national quality register for colorectal cancer. The register has collected data from all patients diagnosed with rectal cancer in Sweden since 1995, and all patients with colon cancer since 2007. The Register includes data on age, gender, ASA classification, treatment, and postoperative follow-up, but lacks data on comorbidity and medical treatment. Completeness of the SCRCR is over 98% for both colon and rectal cancer, and validity data shows an average agreement of 90% (109–111).

The Swedish National Patient Register (NPR) is supervised by the National Board of Health and Welfare. The register contains data on all hospital admissions in Sweden since 1987, including outpatient specialist care visits and outpatient emergency care. It does not, contain data on primary healthcare visits. The validity of the NPR is estimated to be 85–90% (112,113).



Onlay mesh augmentation © Lucy Bai 2021

1.12 IMPLEMENTATION OF A NEW TECHNIQUE

At the Capio S:t Görans Hospital the Donabedians triade structured model is used for quality improvement. The triade states structure, process, and outcome as the three main pillars for improvement (114). The goal is to achieve organisational learning. In this case, we aimed to reduce the rate of complications after midline laparotomies by implementing new methods for opening and closure of the abdomen, especially the suturing technique. The structure included new suturing material, a new surgical routine, and documentation. Following theories originally developed by Argyris (115), we formed double learning loops aimed at organisational learning *i.e.*, incorporation of knowledge and experience into the organisation's structure such that these persist over time despite changes in personnel.
Our work on wound dehiscence started with value stream mapping(116). For this we used the A3 tool (117) - an example of A3 (in Swedish) can be found in Appendix 1.
After value stream mapping we concluded that too many patients developed wound dehiscence. Thus, we collected data from all laparotomies performed during a 6-month period and saw that compared to results in the literature we were doing poorly. After reviewing the literature on abdominal wall closure, we formed a multidisciplinary team including surgeons, a theatre nurse, a surgical assistant nurse, and an external product specialist from a suture company. The team developed a strategy for the implementation of a new suture technique using new material. The strategy included written guidelines for abdominal opening and closure (Appendix 2), including routines for documentation and follow-up. Before implementation several meetings were held with the surgeons and the surgical staff discussing the new routine. Lectures were given by Leif Israelsson, founder of the SSSB technique, and by the suture manufacturer. Feedback from these meetings was incorporated in the guidelines before launching the project. The original trial lasted six months during which time we closely monitored how things were going and were open to changes in routine. To maintain motivation, a small symbolic gift was given as a reward to those surgeons who kept to the guidelines. After six months we the entire staff had adapted to the new technique and it was found both feasible and effective. Since then, loop learning has continued, and we routinely communicate our results back to the staff.

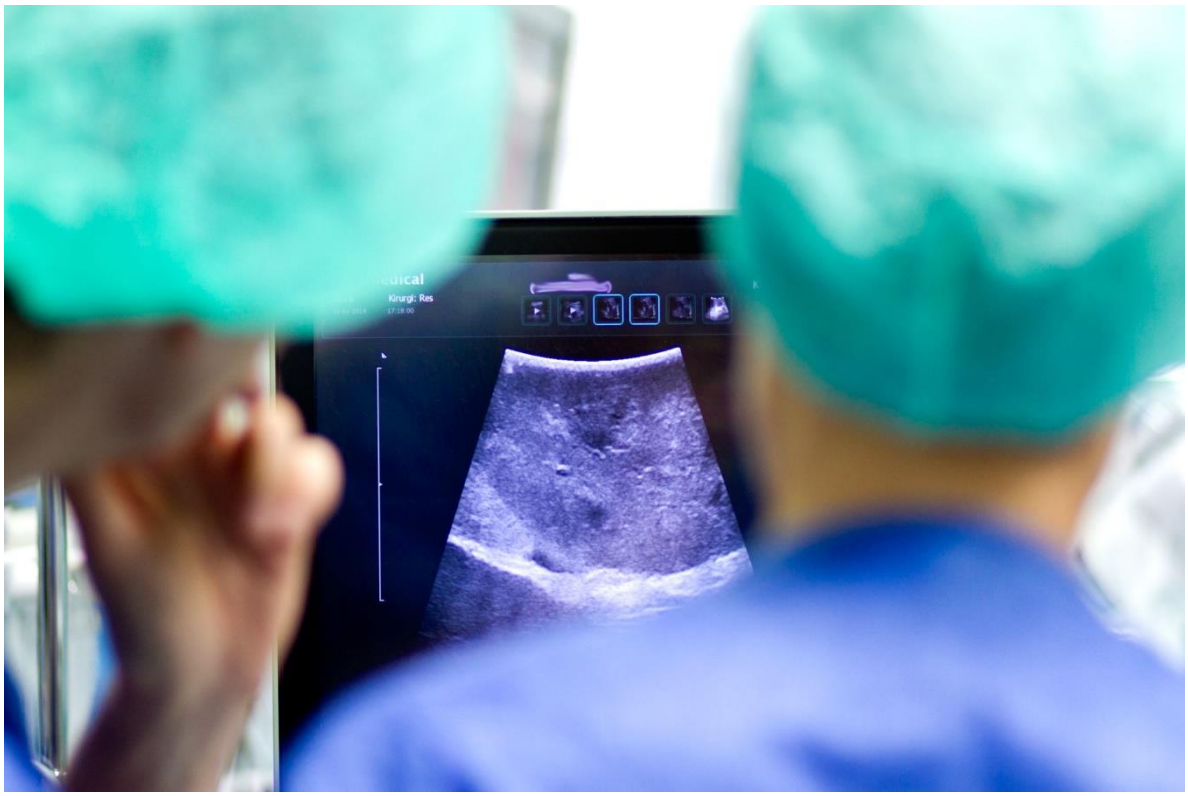
2 PATIENTS AND METHODS

2.1 PAPER 1. SMALL-STITCH-SMALL-BITES TECHNIQUE: A LONG-TERM FOLLOW-UP.

Based on the evidence presented by Milbourn et al, (66,77), Capio S:t Görans Hospital implemented the SSSB technique as standard for midline incision closure. Prior to the new guidelines, abdominal wall closure was according to the preference of the surgeon, which was usually a running polydioxanone (PDS) 0 loop suture on a large needle. No record of layers included or suture length to wound length ratio was made in the surgical report. In the revised local guidelines June 2012, the full SSSB technique was described step by step using 2-0 PDS suture on a small needle, taking small bites in aponeurosis only. It was also obligatory to measure and work out the suture length to wound length ratio and to record these in a separate document. To obtain a deep organisational learning of the new technique we used a double loop learning process (115). Before the implementation, all surgeons were educated in the new technique and got the chance to present their thoughts through local seminars where the technique was discussed. There were guest lectures by experts of the SSSB-technique, and organised self-studies. During the first six months the surgical technique used was monitored closely so that all surgeons cohered. (Delete – repetition!)

This study was a retrospective review of all abdominal surgeries performed 2010-2011 and 2016-2017 at the Department of Surgery, Capio Sankt Göran Hospital, Stockholm. Cases were identified by ICD10 codes JA-JX in the Cambio Cosmic medical records database (118). Laparoscopic cholecystectomy, laparoscopic appendectomy, anal/perianal surgery, and bariatric procedures were excluded. The remaining list was then cleared of all laparoscopic procedures and procedures not performed through a midline incision. In a last step, all cases not fitting the study design, for example where the abdomen was left open, were excluded. The final list was then reviewed by two examiners who scrutinised each patient's records, starting at the index operation extracting data on potential patient-related risk factors and verifying that the procedure was performed through a midline incision. The surgery records were then reviewed to confirm if the study criteria were fulfilled i.e., SSSB with appropriate suture used and the suture length, wound length, and ratio Over 4:1 were correctly noted in the operation records. At the end of the study period, all patient records were reviewed to find postoperative complications or time of death. The endpoint "incisional hernia" was defined as either a clinically evident hernia noted on routine follow-up radiology or visit, incisional hernia accidently diagnosed clinically or by radiology at any other visit to the hospital where the abdomen was examined, or surgery for incisional hernia during the follow-up period. There was no standard protocol for follow-up for all laparotomies since patients were followed up according to the protocols for each disease.

The follow-up of patients in this study included medical records and radiology reports from all contacts with the hospital until 31st March 2020. “Wound dehiscence” was defined as clinically evident fascial dehiscence noted and treated conservatively in the postoperative period, or an acute reoperation for wound dehiscence. End of follow-up for patients in the study was defined as the 31st March 2020, or date of death registered in Cambio Cosmic software, or 31st December the year the patient died in cases where the exact date of death was not known.



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2.2 PAPER 2. INCISIONAL HERNIA AFTER SURGERY FOR COLORECTAL CANCER: A POPULATION-BASED REGISTER STUDY.

This was a population-based cohort study. All procedures for colorectal cancer registered in the Swedish Colorectal Cancer Register (SCRCR) 2007–2013 were identified. Diagnoses from all admissions and visits prior to colorectal cancer resection (identified by the International Classification of Diseases [ICD] code) were retrieved from the National Patient Register (NPR). We identified diagnoses that were generally considered to be risk factors in clinical practice, and collected general descriptive variables including:

- Peripheral vascular disease
- Connective tissue disorder
- Liver cirrhosis
- Renal failure
- Diabetes
- Chronic obstructive lung disease
- Chronic inflammatory condition
- Age
- Body mass index (BMI)
- Gender
- Operation time
- T-category
- Distant metastases
- Preoperative radiation therapy
- Type of incision
- Acute/planned surgery
- Tumour localisation
- Postoperative wound complication
- Adjuvant cytostatic treatment

Cross-matching between the SCRCR and the NPR was performed in 2015 using the Swedish Personal Registration Number, a ten-digit identity number unique for each Swedish citizen (119).

Data on incisional hernias were obtained by combining data from the SCRCR and the NPR. The endpoint incisional hernia was defined as incisional hernia registered in the SCRCR by the surgeon responsible, or ICD codes K43.0–K43.9 for incisional hernia or intervention codes JAD10–JAD87 for surgery for incisional hernia recorded in the NPR. Analyses were performed to assess the impact of each risk factor investigated and to estimate the cumulative incidence of incisional hernia.

2.3 PAPER 3. INCIDENCE OF WOUND DEHISCENCE AFTER COLORECTAL CANCER SURGERY: RESULTS FROM A NATIONAL POPULATION-BASED REGISTER FOR COLORECTAL CANCER.

This study like Study 2 was based on data from the SCRCR combined with data from the NPR on colorectal cancer procedures performed 2007–2013. Patient data and potential risk factors included in the analyses were:

- Peripheral vascular disease
- Connective tissue disorder
- Liver cirrhosis
- Renal failure
- Diabetes,
- Chronic obstructive lung disease
- Chronic inflammatory condition
- Age
- Body mass index (BMI)
- Gender
- Operation time
- T-category
- Distant metastases
- Preoperative radiation therapy
- Type of incision
- Acute/planned surgery
- Tumour localisation
- Postoperative wound complication
- Adjuvant cytostatic treatment

Cross-matching between the SCRCR and the NPR was performed in 2015 using Swedish Personal Registration Numbers.

Data on wound dehiscence were obtained by cross-matching data from the SCRCR and the NPR. The endpoint, wound dehiscence, was defined as either wound dehiscence registered in the SCRCR by the surgeon responsible, or the procedure code for wound dehiscence surgery (JWA00) in the NPR. Analyses were performed to assess the impact of each risk factor investigated and the incidence of wound dehiscence.

2.4 SUBGROUP ANALYSIS OF ACUTE SURGERY BASED ON DATA FROM THE SCRCR

After publication of Papers 2 and 3, where acute and elective surgery were treated as one group, the question was raised whether patients undergoing emergency surgery should be analysed separately in view of the higher risk for complications associated with acute surgery. As a result, an acute surgery subgroup analysis was performed based on the same cohort as in Studies 2 and 3 but including acute surgery only.

2.5 PAPER 4
PROPHYLACTIC RESORBABLE SYNTHETIC MESH TO PREVENT WOUND DEHISCENCE AND INCISIONAL HERNIA IN HIGH HIGH-RISK LAPAROTOMY: A PILOT STUDY OF USING TIGR MATRIX MESH.

The study was performed as a case series of patients from Uppsala University Hospital, the Uppsala Cancer Clinic, and Karolinska University Hospital, Huddinge, who underwent surgery through a midline incision. Inclusion criteria were the presence of at least three documented risk factors for incisional hernia or wound dehiscence. Risk factors investigated in this study were:

- Reoperation
- Age over 80 years
- Generalised malignant decease (presence of distant metastases at the time of surgery)
- COPD Grades III–IV according to the GOLD classification (FEV1 <50% of the expected)
- Serum albumin level <20 g/l
- Sepsis i.e., infection in combination with abnormal values of two or more of the following: body temperature, heart rate, respiratory rate, blood gases, and white blood cell count
- BMI >35
- haemoglobin <80 g/l
- Diabetes with secondary complications (angiopathy, nephropathy, or neuropathy) and insulin treatment
- Steroid treatment (with at least 1 mg betamethasone daily or equivalent) for 7 days preoperatively
- Smoking (at least 10 cigarettes a day for 1 year)
- Chemotherapy (last administration within 2 weeks prior to surgery)
- Irradiation of the abdominal wall.

The abdominal wall incision was closed with continuous Polydioxanon Suture (PDS) with a suture length to incision length ratio of 4:1, using the SSSB technique. After suturing, a

TIGR® Matrix Surgical Mesh was placed in the onlay position over the rectal aponeurosis with an overlap of 5 cm on either side. The mesh was fixated with a continuous PDS 2-0 suture on each side parallel to the midline incision followed by skin closure. All patients were followed up according to routine clinical practice at each unit, but always including a follow-up visit 1 month after surgery. Endpoints in this study were wound dehiscence, wound infection, seroma, and persistent pain.

TIGR® Matrix Surgical Mesh is composed of two different synthetic resorbable fibres having different degradation characteristics. The first fibre, constituting 40% of the matrix, is a copolymer of polyglycolide, polylactide, and polytrimethylene carbonate. The second fibre, making up 60% of the matrix, is a copolymer of polylactide and polytrimethylene carbonate. Both fibres are degraded by bulk hydrolysis, resulting in a decreasing tensile strength caused by loss of fibres. In vitro tests have shown that the first fibre (polyglycolide, polylactide, and polytrimethylene carbonate) loses its functional tensile strength after 2 weeks, and in vivo studies in the abdominal wall of sheep have shown that it is fully absorbed after 4 months (120). Corresponding figures for the second fibre (polylactide and polytrimethylene carbonate) are 9 months and approximately 36 months, respectively. As the first fibre is resorbed, elasticity increases, which improves collagen formation. The TIGR Matrix Surgical Mesh is a resorbable mesh implant, classified as a Class III device in accordance with the European Medical Device Directive (MDD) 93/42/EEC, Annex IX, Section 2.4, Rule 8.

2.6 STATISTICAL METHODS

All statistical calculations were performed using SPSS 22.0-26.0 (Chicago, IL).

Logistic regression was used to study the relationship between predictors (that can be continuous or categorical) and a binary outcome such as incisional hernia. Logistic regression uses the odds of the outcome to fit a curve and calculates odds ratios.

In our studies we used logistic regression to identify possible risk factors from a dataset of multiple variables.

Survival analyses such as logistic regression can investigate predictors and their relationship to a binary outcome. In survival analysis the observation time is included in the analysis which improves the possibility to find survival differences. The Kaplan-Meier Estimator (Kaplan-Meier curve) is a visualisation of the survival function, commonly used in medical statistics to visually compare survival in different groups.

Cox proportions hazard analysis (121) studies the relationship between predictors and the survival time related to a binary outcome. Cox regression calculates survival as a linear function of the individual predictors with results presented as hazard ratios (relative risk). Survival analysis and Cox regression is used in our studies to model the impact of potential risk factors on survival.

2.6.1 Paper 1

Risk factors for wound dehiscence were analysed in uni- and multivariable logistic regression analyses. Variables assumed to be risk factors at the beginning of the study were included in the multivariate analysis. Risk factors for incisional hernia were analysed in uni- and multivariable Cox proportional hazard analysis, adjustment was made for all covariates assumed to increase the risk for development of incisional hernia. Subgroup analyses were performed to investigate risk factors in each group. Potential risk factors were also analysed for the two groups combined. All analyses were performed using the intention-to-treat approach comparing early and late cohorts.

2.6.2 Paper 2

The impact of each potential risk factor on the risk for incisional hernia was evaluated in a survival analysis, applying the date of the primary procedure as the time of entry into the cohort. Date of death or end of follow-up were defined as censored events. Age, body mass index (BMI), and comorbid disease as risk factors for incisional hernia were analysed using Cox proportional hazard analysis. Gender, age, BMI, history of chronic obstructive pulmonary disease, diabetes with secondary complications, chronic renal disease, liver cirrhosis, systemic inflammatory disease, tumour stage category, distant metastases, preoperative radiotherapy, acute/planned surgery, tumour localisation, operation time, postoperative wound complication, and adjuvant cytostatic treatment were included as covariates in the analysis.

2.6.3 Paper 3

The presumed risk factors age, BMI, comorbid disease, presence of distant metastases, and operation time were analysed using univariable and multivariable logistic regression analyses. Survival after reoperation for wound dehiscence was analysed with Cox proportional hazard analysis.

2.6.4 Subgroup analysis of acute surgery based on data from the SCRCR

Difference in outcome between acute and elective surgery was examined with cross-tabulation and Pearson's chi-squared test. Acute surgery as a risk factor for incisional hernia was examined using survival analysis and Cox regression. Wound dehiscence was explored with logistic regression. Risk factors for incisional hernia were examined in univariable and multivariable Cox regression analyses where all suspected risk factors were included. Uni- and multivariable logistic regression was used to examine risk factors for wound dehiscence.

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2.7 ETHICAL CONSIDERATIONS

2.7.1 Papers 1-3

All three studies were based on retrospective data from registers and patient records. Our main ethical considerations were patient integrity and patient autonomy.

In Sweden, there is a great acceptance for using patient registers in decision-making and healthcare allocation. Most patients agree to have their data stored in various registers, and these are used to improve the quality of healthcare. In large retrospective studies such as these, obtaining patient consent would be very time-consuming making them practically impossible. Patient data was anonymised, and the code keys were kept separate from the data sets. All data were stored within hospital walls according to safety regulations. The data sets were processed and presented so that no patient could be recognised.

Paper 1. Approved by the Swedish Ethics Review Authority. Diary number (2019-05787)
Paper 2. Approved by the Regional ethics Review Board in Stockholm ref. (2014/1351-31/5).
Paper 3. Approved by the Regional Ethics Review Board in Stockholm, ref. (2014/1351-31/5).

2.7.2 Paper 4

In this study we evaluated a new medical device. The product itself had already been tested on humans and found to be safe, but this was a new application of the device.

The aim of the study was to improve patient safety i.e., there was a potential benefit for treated patients assuming a decrease in risk for serious complications after surgery. There was, however, a minor risk of discomfort from the mesh augmentation. Our assumption was that patient benefit would outweigh any disadvantage. Informed consent was obtained to ensure patient autonomy.

Paper 4. Approved by the Ethics Review Board of Stockholm ref. (2015/440-31).

3 RESULTS

3.1 PAPER 1

Altogether 1120 midline laparotomies were included in the study, 518 in the study cohort and and 602 in the control cohort. A flow chart of the study assembly is presented in Fig 1. Mean follow-up time was 32 and 73 months in the study and control groups, respectively. Emergency surgery was 60% in both groups. In the study cohort, 481 (93%) had correct SSSB suturing and a satisfactory suture length to wound length ratio (>4) noted in the operation report compared to 7 (1%) in the control cohort. No significant differences in wound dehiscence rates and incisional hernia rates were seen between the two cohorts.

A total of 51 patients developed wound dehiscence, 19 (3,7%) in the study group and 31 (5,1%) in the control group. Of these, 44 required emergency reoperation, 17 in the study group and 27 in the control group. Nine patients (18%) with a documented wound dehiscence later developed an incisional hernia.

Twenty-seven patients (5.2%) in the study group and 33 (5.5%) in the control group developed an incisional hernia. There was no significant difference between the groups. Fig 2 shows the Kaplan- Meier curves for the cumulative incidence of incisional hernia for the two groups. Fig 3 shows a per protocol analysis where patients sutured with SSSB are compared to those closed with the surgeon's method of choice. There was no signifficant difference between these groups. Of the patients with an incisional hernia, 14 in the study group and 21 in the control group required surgery. Surgical site infection (SSI) requiring antibiotic treatment developed in 16 patients (3%) in the study group and 23 (4%) in the control group. This difference was not statistically significant.

Table 2 shows background data and a comparison of the two study cohorts.

In the subgroup multivariable analysis of the study cohort (2016-17), male gender (p=0,011) was a significant risk factor for wound dehiscence. BMI>25 (p=0,007) and wound dehiscence (p=0,003) were risk factors for incisional hernia. Acute surgery, high age, COPD, and previous midline incision did not show a significant association in this group.

Tables 3 and 4 present the results of univariable and multivariable analyses of potential risk factors for incisional hernia and wound dehiscence in the two cohorts combined.

Male gender (p=0.003) and COPD (p=0.022) were significant risk factors for wound dehiscence. History of previous midline incision (p=0.051) and postoperative surgical site infection (p=0.053) showed a tendency to predict wound dehiscence, though not significant at the $p<0.05$ limit.

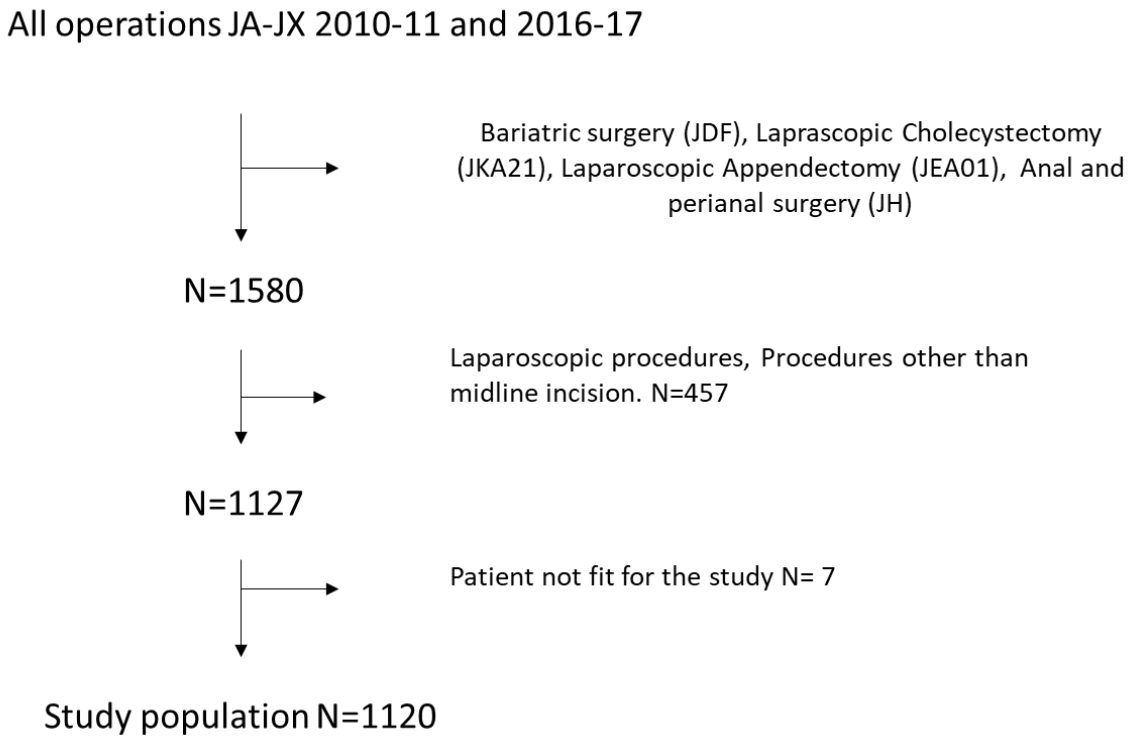


Fig 1 Flow chart of study assembly

Cox regression identified BMI>25 (p=0.002), postoperative wound infection (p=0.001), and wound dehiscence (p<0.001) as independant risk factors for incisional hernia. Figures 4, 5 and 6 show Kaplan-Meier curves for incisional hernia related to the significant risk factors.

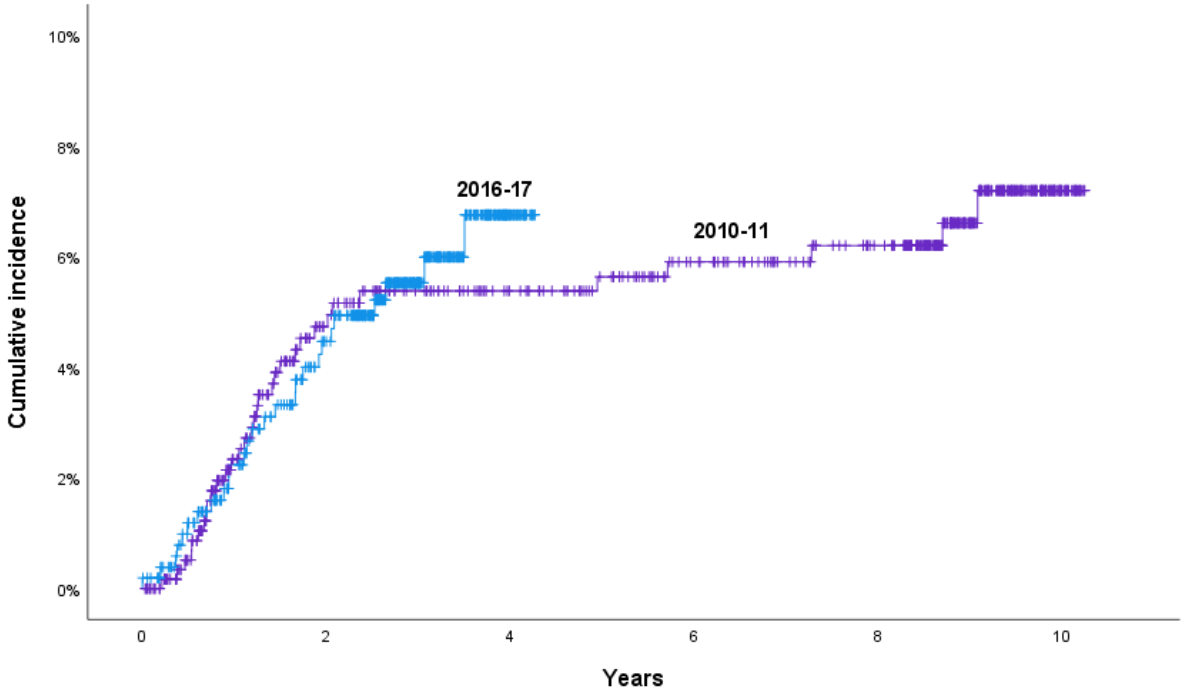


Fig 2 Cumulative incidence of incisional hernia intention-to-treat

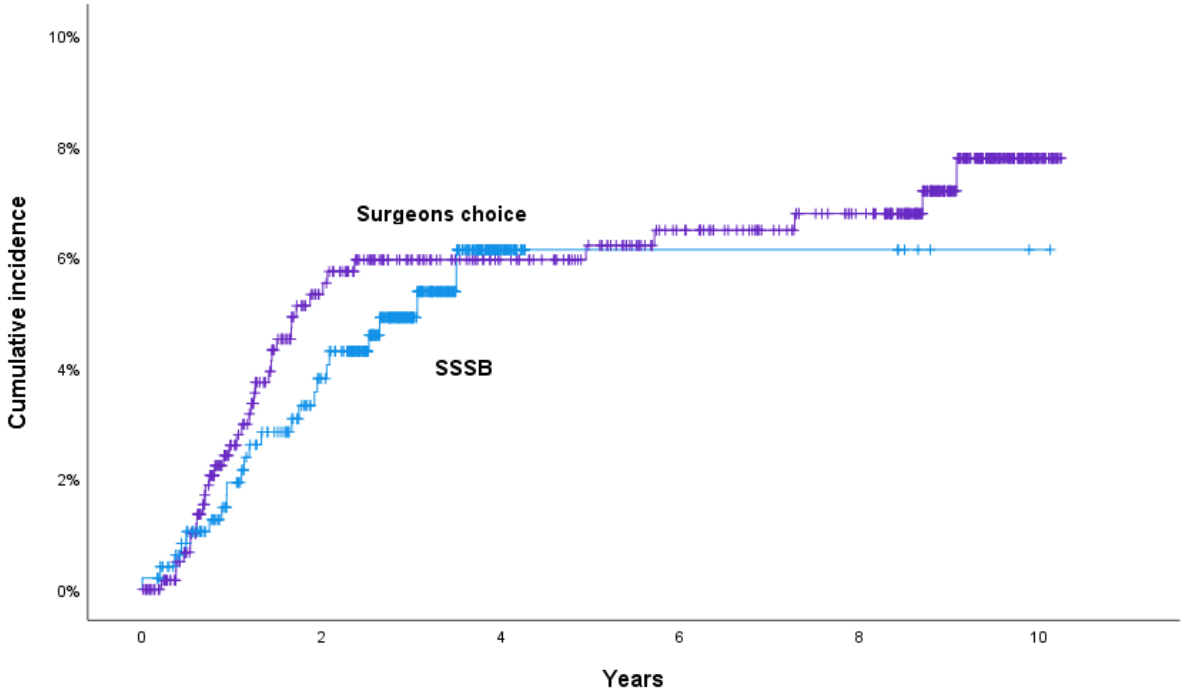


Fig 3 Cumulative incidence of incisional hernia per protocol

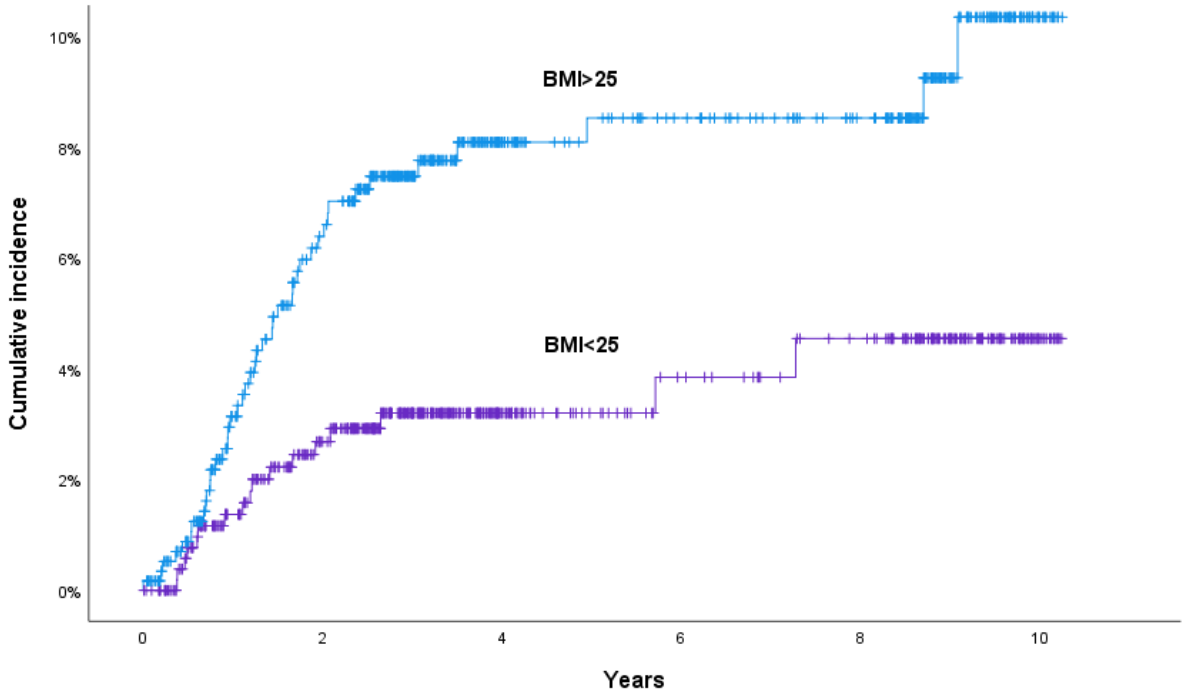


Figure 4. Cumulative incidence of incisional hernia: different BMI categories

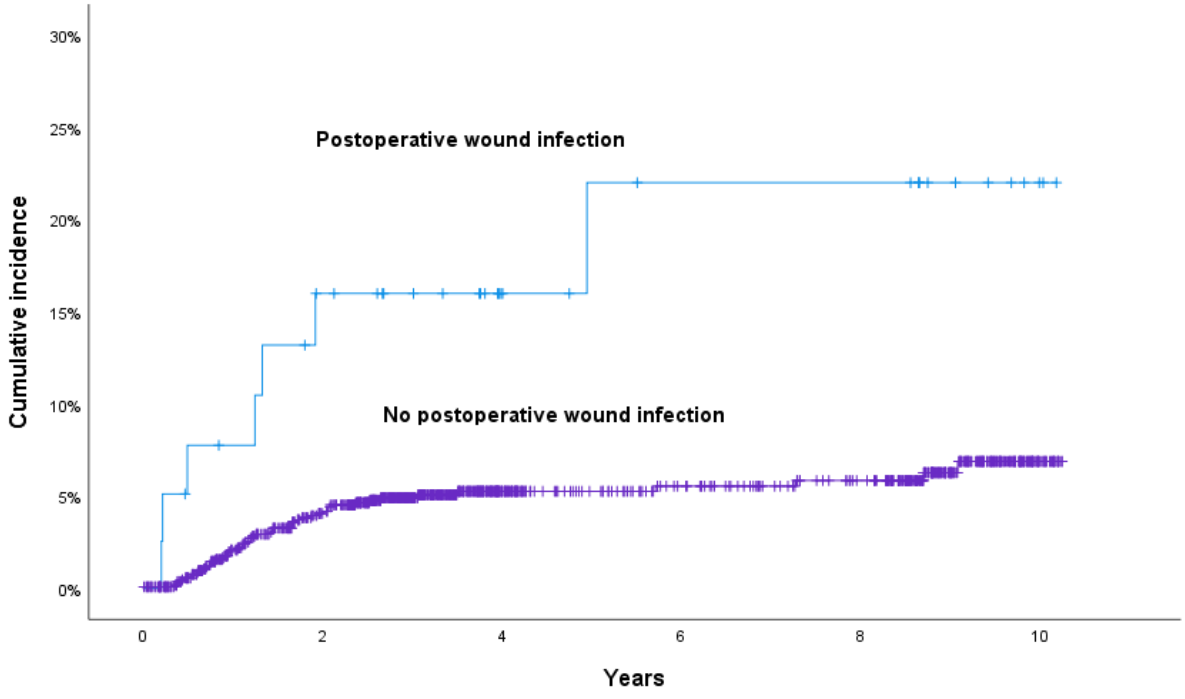


Figure 5. Cumulative incidence of incisional hernia: wound infection or not

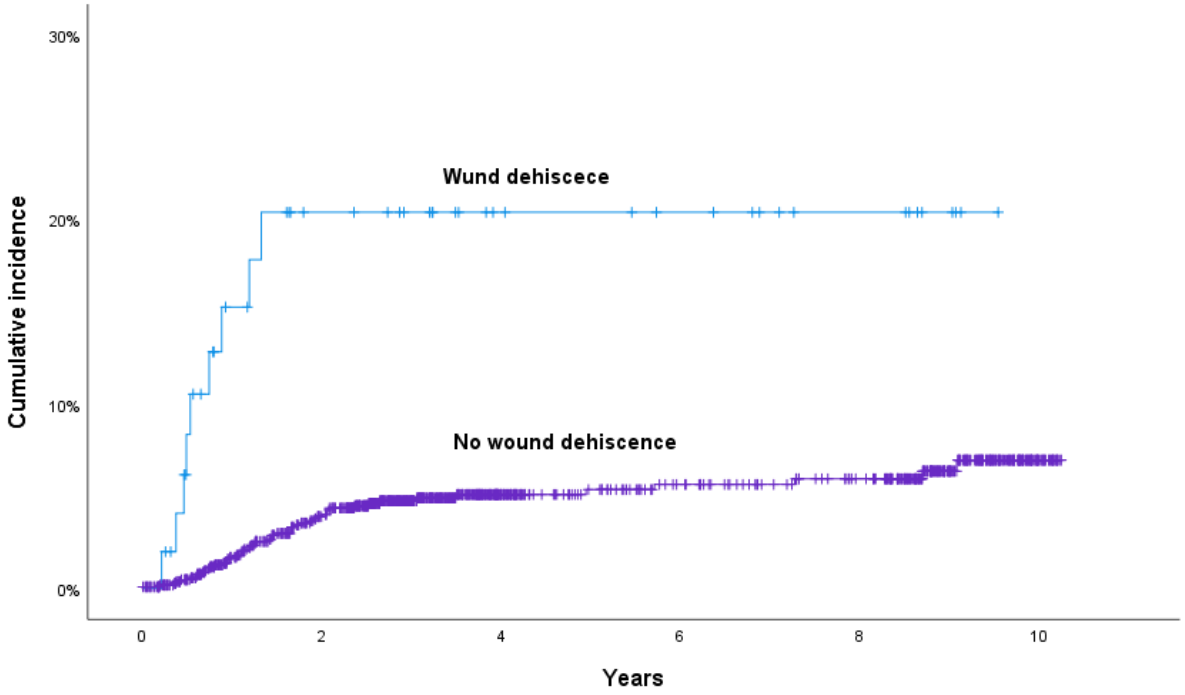


Figure 6. Cumulative incidence of incisional hernia: wound dehiscence or not

Table 2 Background data

Background data	2010-2011	2016-2017	Total
Male	285 (47.3%)	235 (45.4%)	520 (46.4%)
Female	316 (52.5%)	283 (54.6%)	599 (53.5%)
Data on sex missing	1 (0.2%)	0 (0%)	1 (0.1%)
Age (Standard deviation)	70.4 (16.6)	68.3 (16.6)	69.4 (16.6)
Index surgery			
Explorative laparotomy	102 (16.9%)	75 (14.4%)	177 (15.7%)
Stomach and duodenal surgey	20 (3.3%)	16 (3.1%)	36 (3.2%)
Liver and bile duct surgery	5 (0.8%)	0 (0%)	5 (0.4%)
Splenectomy	4 (0.7%)	2 (0.4%)	6 (0.5%)
Colon and small bowel surgery	387 (64.3%)	386 (74.5%)	773 (69%)
Appendectomy	20 (3.3%)	17 (3.3%)	37 (3.3%)
Rectal cancer surgery	52 (8.6%)	19 (3.6%)	71 (6.3%)
Hernia surgery	3 (0.5%)	1 (0.2%)	4 (0.36%)
other	9 (1.5%)	2 (0.4%)	11 (1.0%)
Acute surgery	363 (60.3%)	306 (59.1%)	669 (59.7%)
Elective surgery	239 (39.7%)	212 (40.9%)	451 (40.3%)
BMI (standard deviation)	24.4 (5.0)	24.7 (5.4)	24.5 (5.3)
ASA I	66 (14.1%)	53 (10.9%)	119 (12.4%)
ASA II	189 (40.5%)	184 (37.8%)	376 (39.2%)
ASA III	181 (38.8%)	205 (42.1%)	387 (40.4%)
ASA IV	30 (6.4%)	44 (9.0%)	75 (7.8%)
ASA V	1 (0.2%)	1 (0.2%)	2 (0.2%)
Data on ASA missing	135 (22.4%)	31 (6.0%)	166 (14.8%)
Cronic obstructive pulmonary disease	61 (10.2%)	51 (9.8%)	112 (10%)
Diabetes mellitus	67 (11.1%)	59 (11.3%)	126 (11.2%)
Haemoglobin, g/L (standard deviation)	130 (20)	129 (21)	130 (20)
Albumin, g/L (standard deviation)	26.4 (8.3)	31.0 (7.2)	29.2 (7.9)
C-Reactive Protein, mg/L (standard deviation)	90 (108)	91 (112)	89.9 (109.4)
Previous midline incision	170 (28.4%)	135 (26.1%)	307 (27.4%)
Standardised technique (SSSB) used	7 (1.2%)	481 (93.9%)	491 (44.0%)
Postoperative wound infection	23 (3.8%)	16 (3.1%)	39 (3.5%)

Table 3. Wound dehiscence risk. Univariable and multivariable analyses

	Univariable analysis		**Multivariable analysis**	
	Odds ratio (95% confidence interval)	p	Odds ratio (95% Confidence interval)	p
Primary procedure 2016-2017 (reference category 2010-2011)	0.70 (0.39-1.26)	0.231	0.72 (0.40-1.31)	0.283
Male (ref Women)	1.94 (1.08-3.47)	0.027	2.57 (1.39-4.76)	0.003
Age≥70 yrs (ref Age<70 yrs)	1.78 (0.97-3.26)	0.063	1.02 (0.99-1.03)	0.130
Acute surgery (ref elective surgery)	1.21 (0.67-2.18)	0.526	1.30 (0.71-2.38)	0.399
BMI ≥25 (ref BMI<25)	0.78 (0.44-1.37)	0.385	0,76 (0.43-1.36)	0.361
COPD	2.36 (1.15-4.87)	0.020	2.40 (1.13-5.10)	0.022
Previous midline incision	1.82 (1.02-3.26)	0.043	1.82 (0,999-3.32)	0.051
Postoperative wound infection	2.56 (0.87-7.51)	0.087	2.98 (0.988-8.96)	0.053

Table 4. Incisional hernia Risk. Univariable and multivariable analyses

	Univariable Analysis		**Multivariable Analysis**	
	Hazard ratio (95% Confidence interval)	p	Hazard ratio (95% Confidence interval)	p
Primary surgery 2016-2017 (ref 2010-2011)	1.12 (0.66-1.89)	0.688	1.34 (0.78-2.29)	0.294
Male (ref women)	1.46 (0.88-2.43)	0.148	1.24 (0.71-2.14)	0.440
Age ≥70 yrs (ref age <70 yrs)	0.76 (0.46-1.28)	0.764	1.00 (0.99-1.02)	0.724
Acute surgery (ref elective surgery)	0.72 (0.43-1.19)	0.194	0.72 (0.43-1.21)	0.213
BMI ≥25 (ref BMI<25)	2.34 (1.33-4.10)	0.003	5.45 (1.39-4.33)	0.002
COPD	0.96 (3.38-2.39)	0.925	0.93 (0.36-2.38)	0.878
Previous midline incision	1.55 (0.92-2.62)	0.114	1.52 (0.89-2.59)	0.130
Postoperative wound infection	3.68 (1.67-8.09)	0.001	3.86 (1.73-8.59)	0.001
Wound dehiscence	4.81 (2.36-9.81)	0.000	5.00 (2.39-10.48)	0.000

3.2 PAPER 2

Between 2007 and 2013, 39 984 patients were registered in the SCRCR. After excluding laparoscopic procedures, procedures repeated on the same patient, procedures with concomitant liver resection, and procedures without laparotomy, 28 913 patients remained in the study. The study cohort assembly flow chart is shown in Figure 7. Baseline characteristics of the study population are shown in Table 5. In all, 1352 (cumulative incidence 4,7 %) patients were either diagnosed with an incisional hernia or underwent surgery for incisional hernia. In the multivariate analysis, risk for incisional hernia was increased in males, long operation time (exceeding 180 min), age < 70 years, BMI > 30 and postoperative wound complication. Table 6 shows the results of the uni- and multivariable analyses of risk factors. Figures 8-12 shows the Kaplan-Meier curves for the significant risk factors. History of comorbid disease, tumour stage, tumour localisation, preoperative radiotherapy, adjuvant chemotherapy, postoperative bleeding, and acute/elective surgery had no statistically significant impact.

In an additional analysis performed after publication, wound dehiscence instead of postoperative wound complication was analysed as risk factor. Wound dehiscence was seen to be a statistically significant risk factor for incisional hernia, hazard ratio 3.04 [95%CI 2.95-3.93] p<0.001. The Kaplan-Meier curve for wound dehiscence related to incisional hernia is added as Figure 13.

Figure 7. Flow chart of cohort assembly Study 2

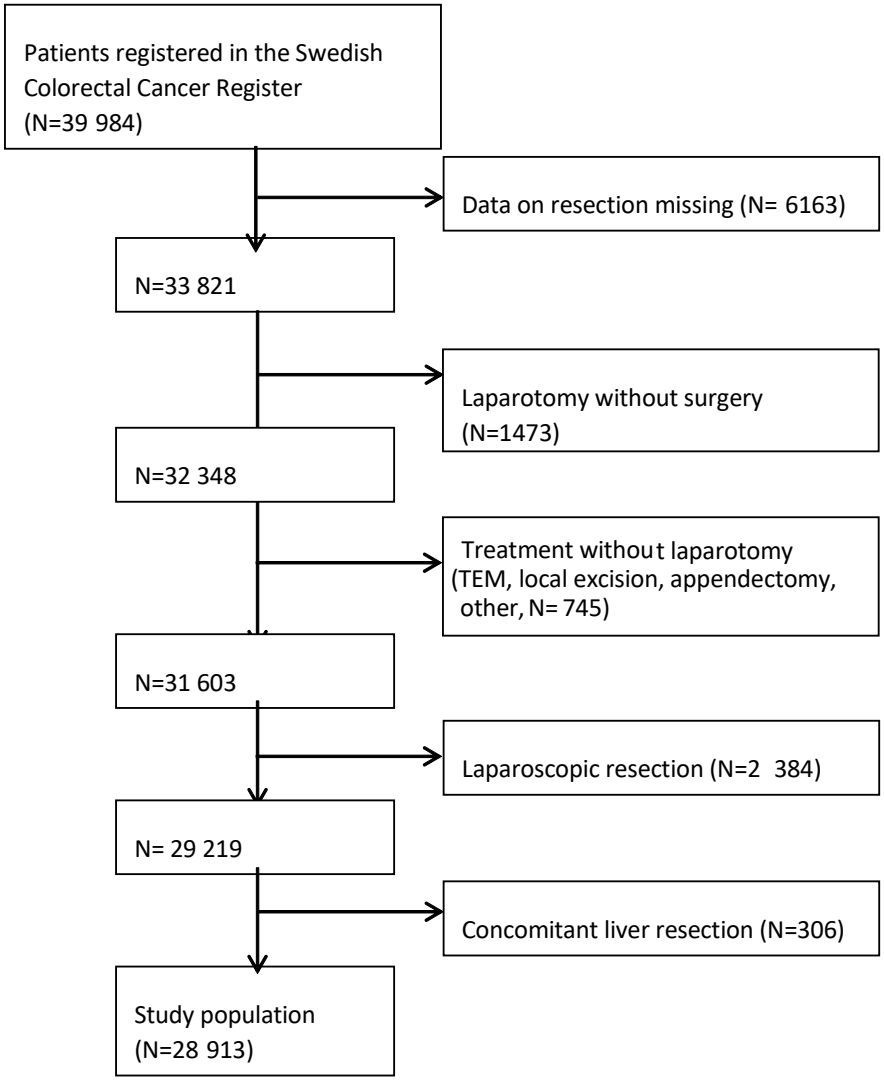


Table 5. Baseline characteristics, study 2

Mean age, years (standard deviation)	71.1 (11.5)
Gender	
Men	14 986 (51.8%)
Women	13 927 (48.2%)
T	
0	292 (1.0%)
I	1585 (5.5%)
II	4595 (15.9%)
III	16920 (58.5%)
IV	5333 (18.4%)
TX/unknown	188 (0.6%)
N	
0	15904 (55.0%)
I	7152 (24.7%)
II	5491 (19.0%)
NX/unknown	366 (1.2%)
M	
0	24 207 (83.7%)
I	3606 (12.5%)
MX/unknown	1200 (3.8%)
Treatment	
Resection of ascending colon (including ileocecal resection)	10666 (36.9%)
Resection of descending colon (including sigmoid colon)	8544 (29.6%)
Resection of rectum (anterior resection and abdominoperineal resection)	8271 (28.7%)
Other (including resection of transverse colon and total colectomy)	1432 (5.0%)
Stomy	
Temporary	4307 (15.0%)
Permanent	6083 (21.2%)

Table 6. Univariable and multivariable Cox proportional hazard analysis of risk for incisional hernia.

		Univariable Cox proportional hazard analysis		Multivariable Cox proportional hazard analysis	
Variable	**N**	**Hazard ratio (95% confidence interval)**	**p**	**Hazard ratio (95% confidence interval)**	**p**
Gender					
Women (ref)	13 927 (48.2%)				
Men	14 986 (51.8%)	1.47 (1.29-1.67)	<0.001	1.40 (1.21-1.62)	<0.001
Age					
>70 years (ref)	16 205 (56.0%)				
≤70 years	12 704 (43.9%)	1.59 (1.37-1.82)	<0.001	1.34 (1.16-1.56)	<0.001
Data on age missing	4 (<0.1%)				
BMI					
<30	20 769 (71.8%)				
≥30	4 036 (14.0%)	1.94 (1.65-2.22)	<0.001	1.78 (1.51-2.09)	<0.001
Data on BMI missing	4 108 (14.2%)				
Chronic Obstructive Pulmonary disease					
No	27 600 (95.5%)				
Yes	1 313 (4.5%)	1.29 (0.94-1.76)	0.112		
Diabetes with sec complications					
No	28 011 (96.9%)				
Yes	902 (3.1%)	0.74 (0.46-1.20)	0.225		
Chronic kidney disease					
No	28 309 (97.9%)				
Yes	604 (2.1%)	0.87 (0.48-1.58)	0.656		
Liver cirrhosis					
No	28 841 (99.8%)				
Yes	72 (0.2%)	2.67 (1.08-7.67)	0.035		
Systemic inflammatory disease					
No	28 376 (98.1%)				
Yes	537 (1.9%)	1.10 (0.66-1.83)	0.725		
Adjuvant chemo					
No	23 206 (80.3%)				
Yes	5 707 (19.7%)	1.14 (0.97-1.34)	0.103		

		Univariable Cox proportional hazard analysis		Multivariable Cox proportional hazard analysis	
Variable	**N**	**Hazard ratio (95% confidence interval)**	**p**	**Hazard ratio (95% confidence interval)**	**p**
T					
1 (ref)	1 585 (5.5%)				
0	292 (1.0%)	0.94 (0.45-1.98)	0.873		
2	4 595 (15.9%)	1.13 (0.83-1.54)	0.439		
3	16 920 (58.5%)	1.01 (0.76-1.34)	0.954		
4	5 333 (18.4%)	0.99 (0.71-1.40)	0.987		
TX/unknown	188 (0.7%)	1.21 (0.48-3.03)	0.684		
Distant metastases					
No (ref)	26 348 (91.1%)				
Yes	2 565 (8.9%)	0.94 (0.70-1.27)	0.701		
Preoperative radiotherapy					
No	22 988 (79.5%)				
Yes	5 897 (20.4%)	1.35 (1.16-1.57)	<.001		
	28 (0.1%)				
Acute/planned surgery					
Planned	24 520 (84.8%)				
Acute	4 386 (15.2%)	1.04 (0.85-1.28)	0.686		
Data on acute/planned surgery	7 (<0.1%)				
Tumor localization					
Colon	20 642 (71.4%)				
Rectum	8 271 (28.6%)	1.43 (1.25-1.64)	<0.001		
Operative time					
<180 minutes	13 509 (46.7%)				
≥180 minutes	14 426 (49.9%)	1.50 (1.31-1.72)	<0.001	1.25 (1.08-1.45)	0.003
Data on operative time missing	978 (3.4%)				
Postoperative wound complication					
No	27 142 (93.9%)				
Yes	1 771 (6.1%)	2.29 (1.88-2.79)	<0.001	2.09 (1.70-2.58)	<0.001
Postoperative bleeding and/or transfusion					
No	28 630 (99.0%)				
Yes	283 (1.0%)	0.77 (0.35-1.73)	0.533		

Figure 8 Cumulative incidence of incisional hernia: gender

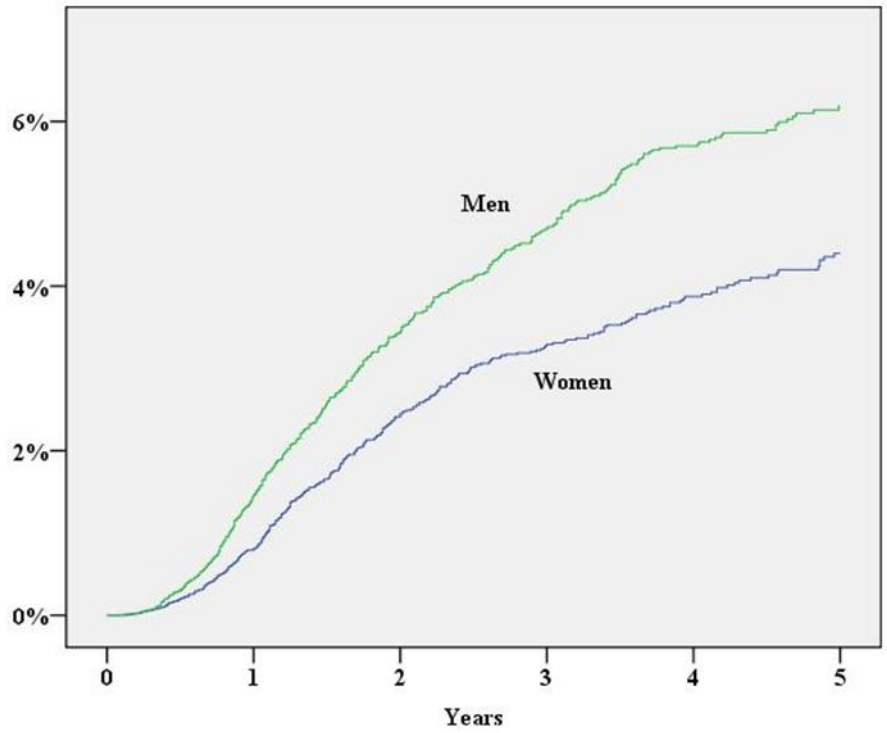


Figure 9 Cumulative incidence of incisional hernia: operation time

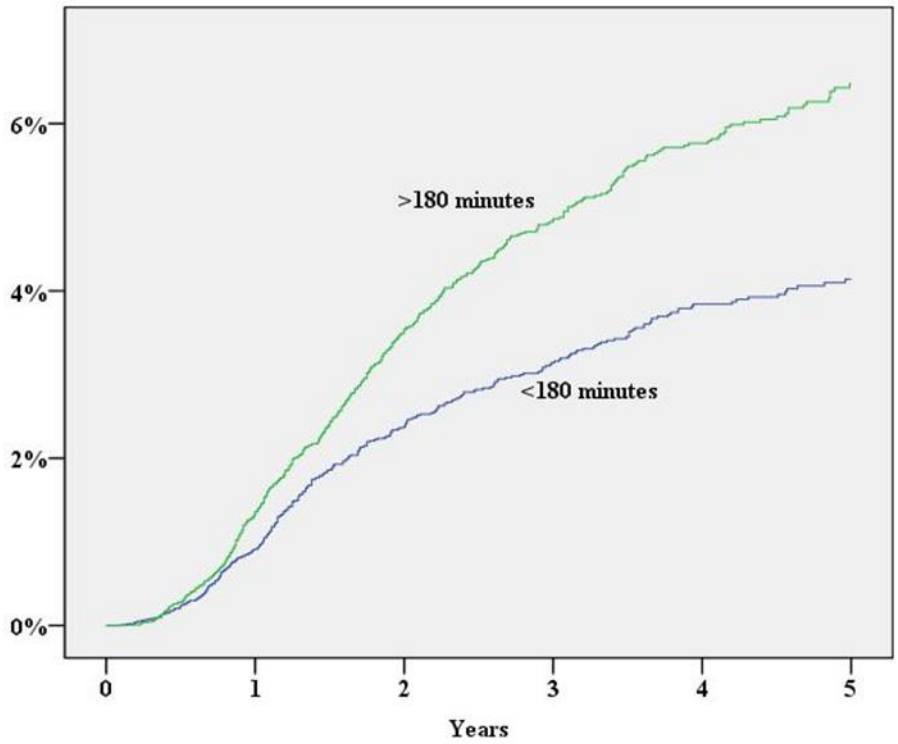


Figure 10 Cumulative incidence of incisional hernia: age

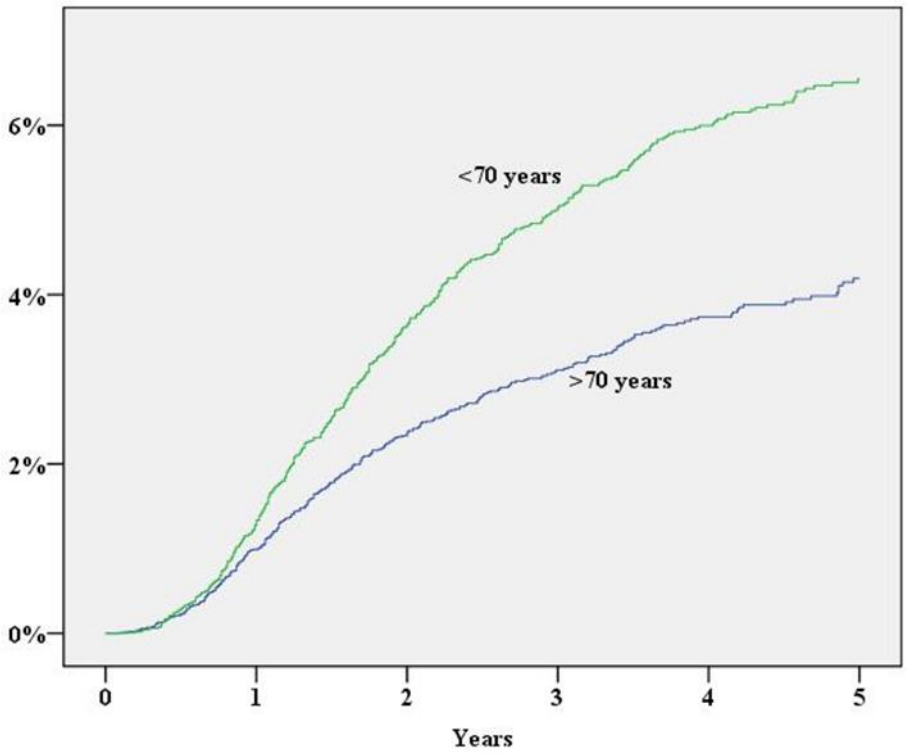


Figure 11 Cumulative incidence of incisional hernia: BMI

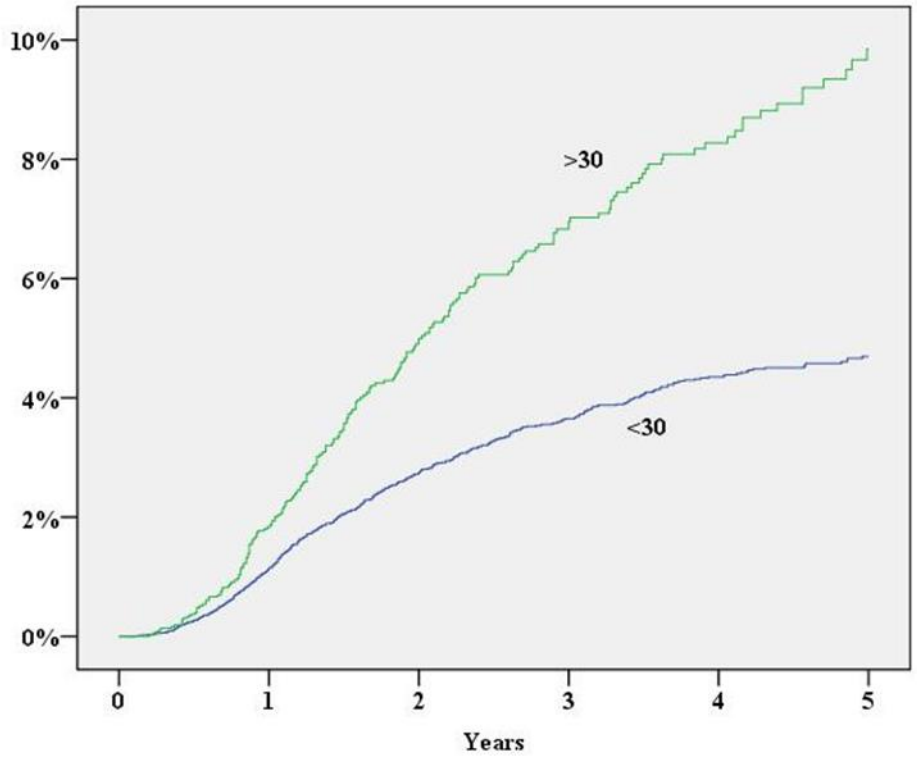


Figure 12 Cumulative incidence of incisional hernia: wound complication

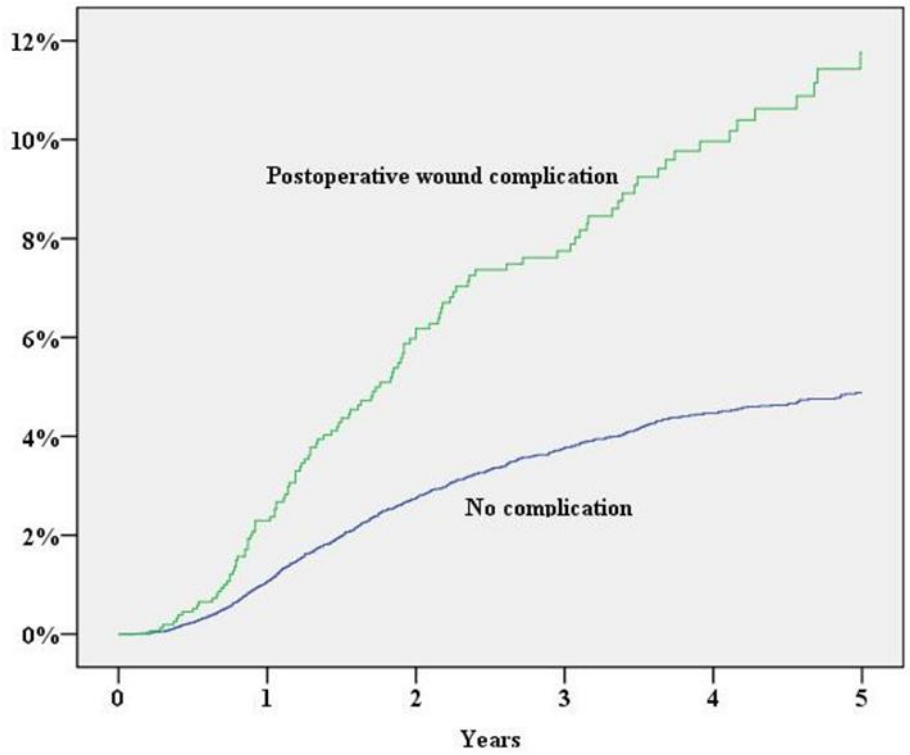
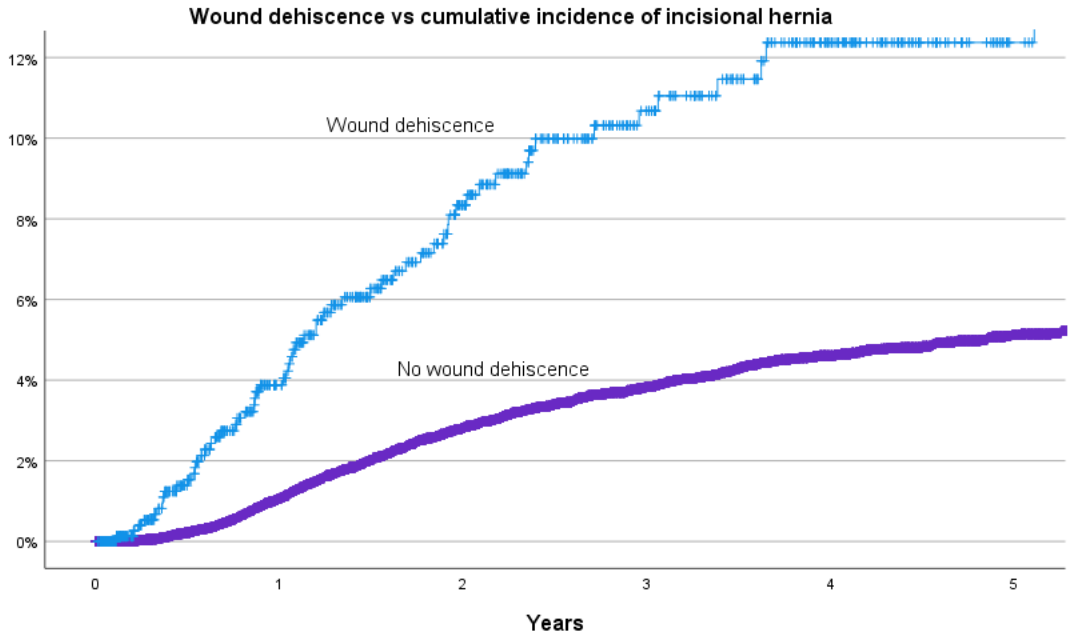


Figure 13 Cumulative incidence of incisional hernia: wound dehiscence



3.3 PAPER 3

Between 2007 and 2013, 39 984 patients were registered in the SCRCR. After excluding patients who had not undergone surgery, patients on whom data on the procedure were missing, laparoscopic procedures, appendectomies, transluminal endoscopic mucosectomies, and local excisions, 30 505 patients remained in the study group. The flowchart for the cohort assembly is shown in Figure 14. Baseline characteristics of the study population are shown in Table 7.

The incidence of reoperation for wound dehiscence was 2.9%. In multivariable regression, age > 70 years, male gender, BMI > 30, history of chronic obstructive pulmonary disease, history of generalised inflammatory disease, and operation time less than 180 min were found to be independent risk factors for wound dehiscence. Results of the uni- and multivariable logistic regression analyses are presented in Table 8.

The single strongest risk factor was male gender (odds ratio 3.00; 95% confidence interval 2.52–3.57). Diabetes, chronic renal disease, liver cirrhosis, and distant metastases had no impact on the risk for wound dehiscence. In univariable Cox regression analysis, the hazard ratio for postoperative death was 1.24 (95% confidence interval 1.12–1.38, $p < 0.001$) for patients that needed reoperation for wound dehiscence. When adjusting for the risk factors found to have a significant association with wound dehiscence, the hazard ratio was 1.26 (95% confidence interval 1.11–1.43, $p < 0.001$). Fig15 shows Kaplan-Meier curves for overall survival of patients that needed surgery for wound dehiscence and those who did not.

Figure 14. Flow chart of cohort assembly

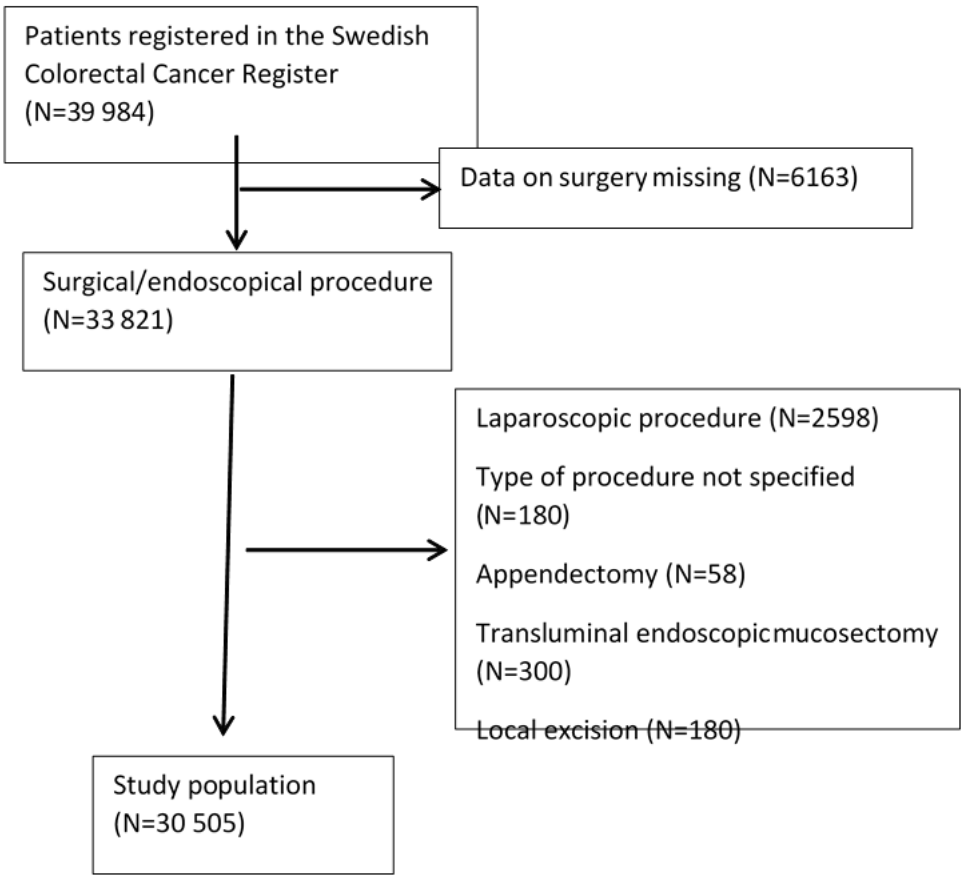


Table 7. Patient characteristics, Study 3

Mean age, years (standard deviation)	71.1 (11.6)
Gender	
Male	15 820 (51.9%)
Female	14 685 (48.1%)
BMI≥30	4160 (13.6%)
Chronic obstructive pulmonary disease	1383 (4.5%)
Complicated diabetes	952 (3.1%)
Chronic kidney disease	632 (2.1%)
Liver cirrhosis	78 (0.3%)
Generalised inflammatory disease	558 (1.8%)
Mean operation time, minutes (standard deviation)	207 (115)
TNM classification*	
T	
0	297 (1.0%)
I	1594 (5.2%)
II	4623 (15.2%)
III	17166 (56.3%)
IV	5746 (18.8%)
TX/unknown	1079 (3.5%)
N	
0	16046 (52.6%)
I	7302 (23.9%)
II	5697 (19.0%)
NX/unknown	1460 (4.8%)
M	
0	24537(83.7%)
I	4649 (12.5%)
MX/unknown	1319 (4.3%)

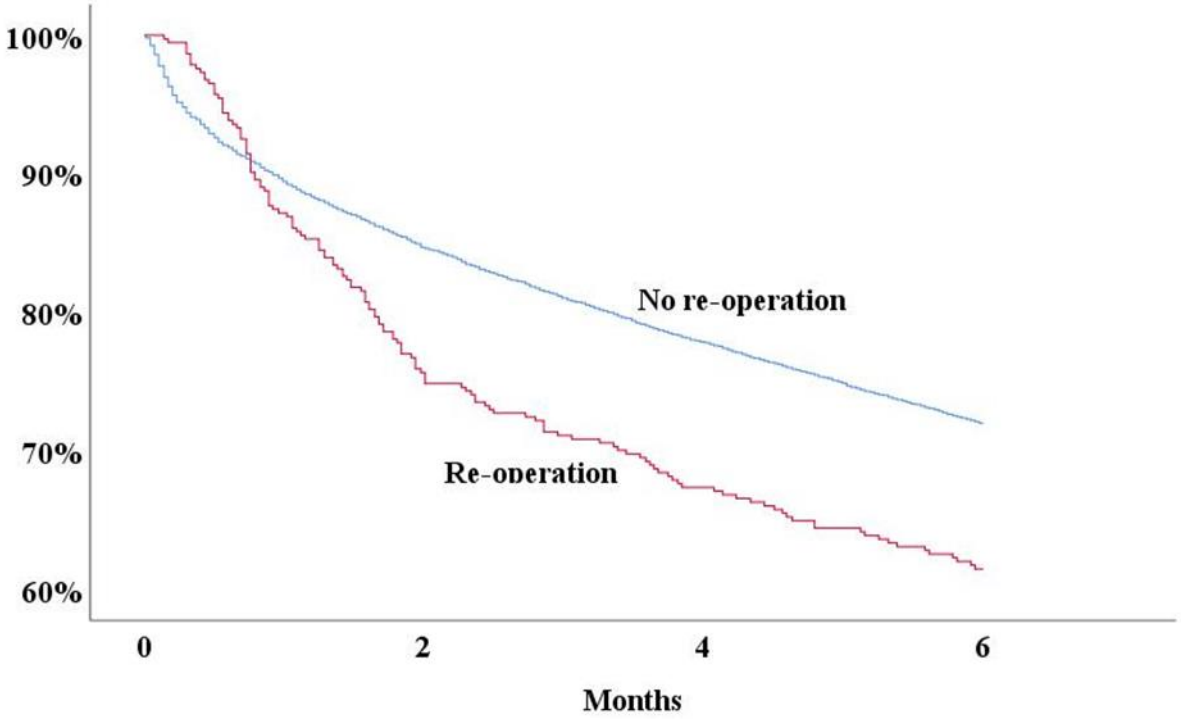
* TNM staging system colorectal cancer. (122)

Table 8. Univariable and multivariable logistic regression analyses with wound dehiscence as outcome.

		Univariable logistic regression analysis		Multivariable logistic regression analysis	
Variable	**N**	**Odds ratio (95% confidence interval)**	**p**	**Odds ratio (95% confidence interval)**	**p**
Gender					
Female (ref)	244/14685 (1.7%)				
Male	649/15820 (4.1%)	2.53 (2.18-2.94)	<0.001	3.00 (2.52-3.57)	<0.001
Age					
≤70 years	287/13420 (2.1%)				
>70 years (ref)	606/17081 (3.5%)	1.68 (1.46-1.94)	<0.001	1.72 (1.46-2.02)	<0.001
Data on age missing	0/4 (0%)				
BMI					
<30	543/21700 (2.5%)				
≥30	184/4160 (4.4%)	1.80 (1.52-2.14)	<0.001	1.98 (1.66-2.36)	<0.001
Data on BMI missing	166/4645 (3.6%)				
Chronic obstructive pulmonary disease					
No	809/29122(2.8%)				
Yes	84/1383 (6.1%)	2.26 (1.80-2.85)	<0.001	1.98 (1.52-2.58)	<0.001
Complicated diabetes					
No	863/29553 (2.9%)				
Yes	30/952 (3.2%)	1.08 (0.75-1.57)	0.677		
Chronic renal disease					
No	870/29873 (2.9%)				
Yes	23/632 (3.6%)	1.26 (0.83-1.92)	0.284		

		Univariate logistic regression analysis		**Multivariate logistic regression analysis**	
Variable	N	Odds ratio (95% confidence interval)	p	Odds ratio (95% confidence interval)	p
Liver cirrhosis					
No	890/30427 (2.9%)				
Yes	3/78 (3.8%)	1.33 (0.42-4.22)	0.631		
Generalised inflammatory disease					
No	861/29947 (2.9%)				
Yes	32/558 (5.7%)	2.01 (1.43-3.00)	<0.001	2.27 (1.49-3.45)	<0.001
Liver and/or lung metastases					
Yes	85/3372 (2.5%)				
No	808/27133 (3.0%)	0.84 (0.67-1.06)	0.138		
Operation time					
≥180 minutes	402/14754 (2.7%)				
<180 minutes	455/14525 (3.1%)	1.16 (1.008-1.32)	0.039	1.36 (1.17-1.59)	<0.001
Data on operation time missing	36/1226 (2.9%)				

Figure 15. Overall survival of patients undergoing and those not undergoing reoperation for wound dehiscence.



3.4 SUBGROUP ANALYSIS OF ACUTE SURGERY BASED ON DATA FROM THE SCRCR

In the Study 2 cohort, 4386 (15,2%) of 24 520 had acute primary surgery. The cumulative incidence of incisional hernia was 3.81% for acute surgery and 4.82% in the elective surgery group (p=0,04). In survival analysis, there was no significant difference between the groups (p=0.735). The Kaplan-Meier curve comparing acute and elective surgery is shown in Fig16. BMI>30 (p=0.02) and wound dehiscence (p=0.00) were significant risk factors for development of incisional hernia in the acute surgery group. The results of the uni- and multivariable Cox regression analyses are presented in Table 9. Figs 17 and 18 show the survival functions? for BMI and wound dehiscence related to incisional hernia.

In the Study 3 cohort, 5027 patients (16,5%) of the 30 505 underwent acute surgery. The cumulative incidence of wound dehiscence was 4.0% following acute surgery and 2.8% following elective surgery (p<0.01). In a logistic regression analysis, acute surgery was seen to be a significant risk factor for wound dehiscence (odds ratio 1.4 [95 % confidence interval 1.2-1.7] P<0.01). In multivariable logistic regression analysis, male gender (p=0,00) and COPD (p=0.03) were significant risk factors for wound dehiscence development in the acute surgery group. The results of the uni- and multivariable logistic regression analyses are presented in Table 10.21.

Fig 16 cumulative incidence of incisional hernia

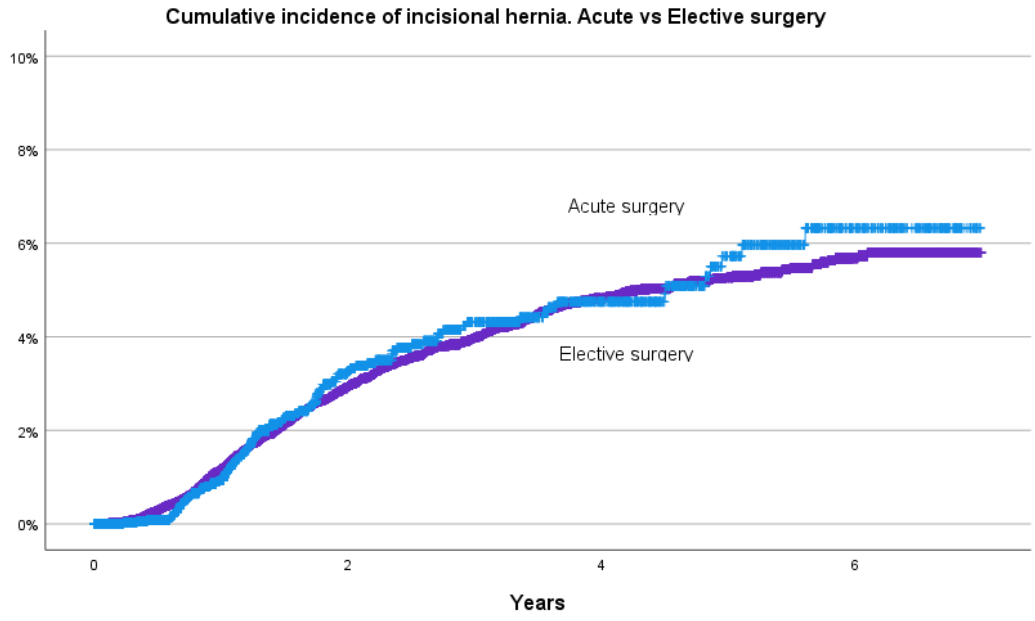


Fig 17 Cumulative incidence of incisional hernia (Acute surgery): BMI

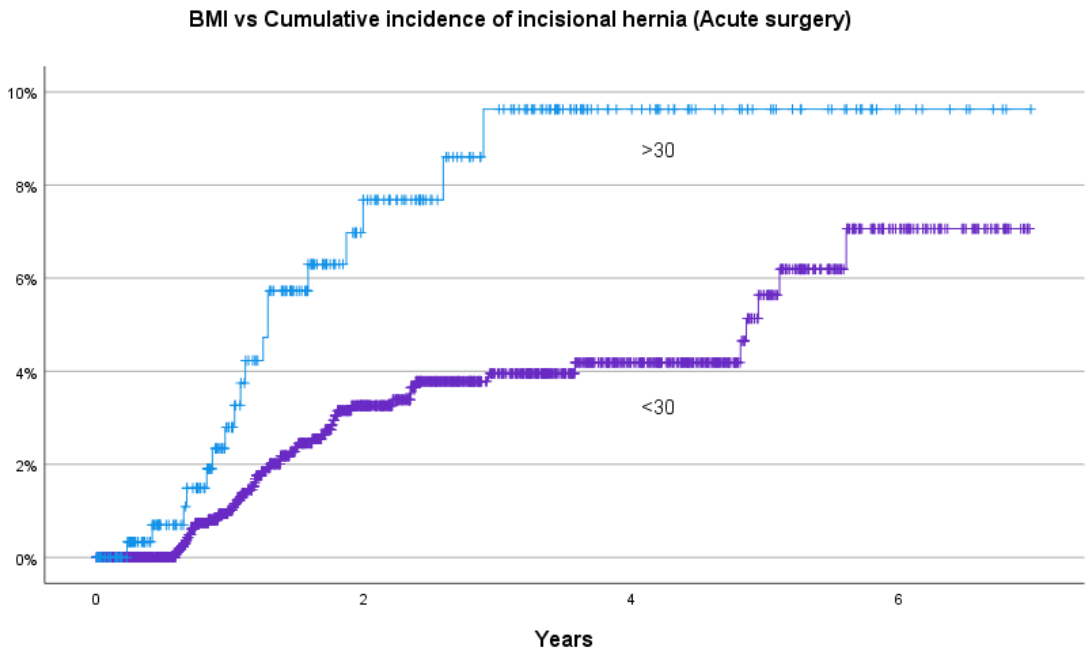


Fig 18 Cumulative incidence of incisional hernia (Acute surgery): wound dehiscence

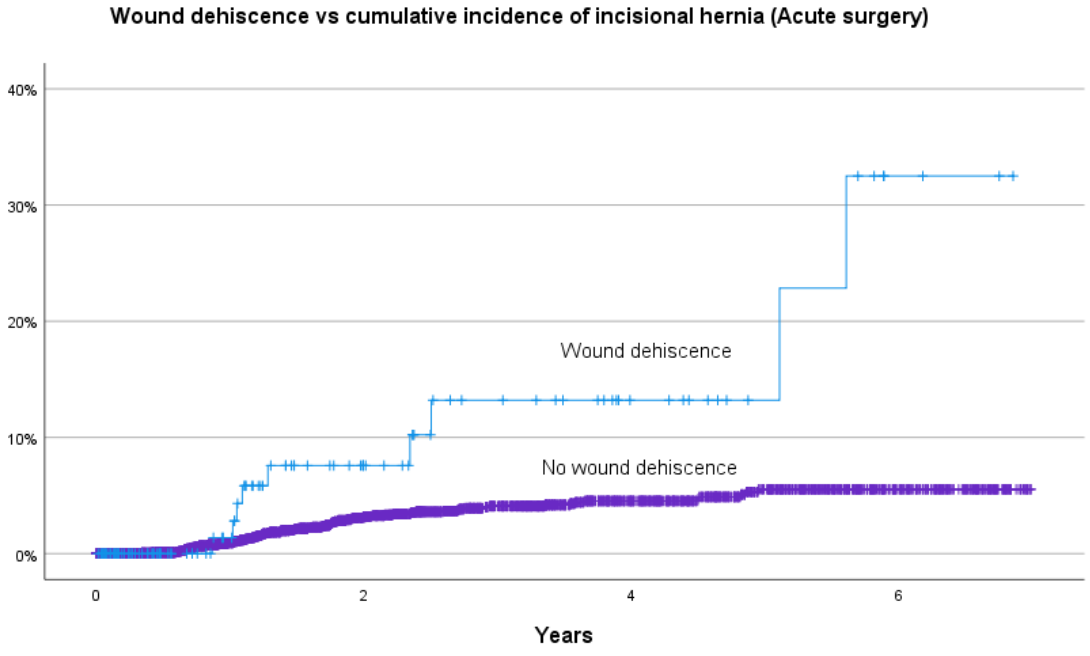


Table 9 Univariable and multivariable Cox regression analyses of risk factors for incisional hernia

Cox regression analyses of risk factors for Incisional hernia.				
	Hazard ratio		Hazard ratio	
	Univariate	p	Multivariate	p
BMI>30	2.2 (1.3-3.8)	0.04	1.97 (1.1-3.5)	0.02
Wound dehiscence	3.7 (1.9-7.4)	0.00	4.8 (2.1-10.8)	0.00
Age >70 years old	0.50 (0.34-0.75)	0.001	0.65 (0.39-1.1)	0.08
Male gender	1.5 (1.0-2.2)	0,033	1.3 (0.8-2.2)	0.240
Operation time >180 min	1.4 (0.9-2.0)	0.095	1.0 (0.6-1.8)	0.733
Postoperative wound complication	2.3 (1.3-4.4)	0.007	1.9 (0.8-4.1)	0.12
COPD	0.80 (0.25-2.52)	0.699	0.62 (0.14-2.66)	0,52
Diabetes	2.3 (0.85-6.3)	0.103	2.9 (0.9-9.6)	0.071

Table 10 Univariable and multivariable logistic regression analyses of risk factors for wound dehiscence

Logistic regressions analysis of risk factors for Wound dehiscece				
	Odds ratio		Odds ratio	
	Univariate	P	Multivariate	P
BMI >30	1.4 (0.9-2.3)	0.18	1.58 (0.9-2.7)	0.09
Diabetes	0.70 (0.26-1.9)	0.49	0.25 (0.03-1.8)	0.17
COPD	2.16 (1.3-3.5)	0.02	2.1 (1.1-3.9)	0.03
Male gender	2.10 (1.6-2.8)	0.00	2.3 (1.6-3.5)	0.00
Age >70 years old	1.38 (1.0-1.9)	0.037	1.0 (1.00-1.04)	0.01
Operation time >180 min	1.00 (0.74-1.4)	0.99	0.72 (0.48-1.08)	0.11

3.5 PAPER 4

Sixteen patients were included in the study. Baseline data and outcome are presented in

Table 11. Most of the patients underwent peritonectomy with hyperthermic intraperitoneal chemotherapy (HIPEC) for peritoneal metastases. Mean follow-up time in the study was 9 months. Of the 16 patients, 1 had a seroma that needed drainage and antibiotic treatment and 1 had a wound infection that needed antibiotic treatment. There was no complication requiring reoperation. No wound dehiscence or incisional hernia was seen. None of the participating surgeons found the onlay mesh fixation technically difficult or time-consuming. There were no major complaints from patients regarding discomfort related to the mesh.

Table 11. Study group, Study 4

Patient	Sex	Age (years)	Operating Unit	Indication for surgery	Risk factors	Adverse Events	Comments
1	M	42	UCC	PM+AWM	E+I+K	-	
2	F	49	UCC	PM	B+E+I+K	-	
3	F	58	UCC	PM	A+B+C+E+I	-	
4	F	65	UCC	PM+AWM	E+I+K	-	
5	F	65	UCC	PM+AWM	E+F+K	-	
6	F	65	UCC	PM+AWM	E+I+K	-	
7	F	63	UCC	PM+AWM	E+I+K	-	
8	F	55	UCC	PM+AWM	E+I+K	-	
9	F	70	UCC	PM+AWM	E+I+K	-	
10	F	67	UCC	PM+AWM	A+D+E+I+K	Seroma	Drain + AB
11	F	45	UCC	PM+AWM	B+E+I+K	-	
12	M	32	UUH	Pancreatic cancer	B+K	-	
13	M	77	Huddinge	Reoperation for dehiscence	G+H+I	-	
14	M	78	Huddinge	Reoperation for dehiscence	G+H+I+J	Superficial wound Infection	AB
15	F	69	Huddinge	Reoperation for dehiscence	B+F+I+L	-	
16	M	67	Huddinge	Reoperation for dehiscence	B+D+F	-	

PM = Peritoneal Metastases, AWM = Abdominal Wall Metastases, UCC= Uppsala Cancer Clinic, UUH=Uppsala University Hospital AB = Antibiotic Treatment

Risk factors: A.COPD; B.BMI > 35; C.Insulin-treated diabetes; D. Smoking; E. Ongoing/previous cytostatic treatment: F. Laparotomy + GI resection < 1month previously; G. Reoperation; H. Acute surgery; I. Generalised cancer; J. Albumin < 20 g/L; K. Abdominal wall resection; L. Steroid treatment.

4 DISCUSSION

4.1 GENERAL COMMENTS

Incisional hernia and wound dehiscence are midline incision complications that share the same pathogenesis i.e., impaired healing of the rectus aponeurosis. My clinical experience, which is also supported by the findings in this thesis, is that the most vulnerable patients with severe comorbidity develop acute wound dehiscence, whereas younger and stronger patients endure the postoperative period and develop an incisional hernia at a later stage. There are well-established methods to prevent these complications, meticulous suturing technique being alternative number one. In second place, prophylactic mesh augmentation may further reduce complications. However, for reasons of cost and time consumed, I do not think prophylactic mesh implantation should be standard practice but preserved for patients at high risk for impaired wound healing. All surgeons should be aware of these risk factors and use stratification tools in the preoperative workup to identify those patients likely to benefit from mesh reinforcement of the abdominal wall.

This thesis studies open surgery through a midline incision, thus ignoring one important solution to the problem. Laparoscopic surgery has significantly lower risk for incisional hernia (123,124) and there is also strong evidence that fascial dehiscence is less common after laparoscopic surgery (125). Furthermore, laparoscopic surgery has other benefits such as shorter hospital stay, less need for opioid treatment etc.

However, there will still be cases where open surgery via a midline incision is indicated.

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4.2 IMPLEMENTATION OF SSSB AT S:T GÖRANS HOSPITAL.

The structured implementation of the SSSB technique in clinical practice at S:t Görans Hospital led to high compliance to use of the technique that remained four years later. In our study, 93% of midline incisions were closed using a correct SSSB technique and accurately registered in the surgical report. In a similar study, Tolstrup et al report 73% compliance to the technique (126). However, in a questionnaire study by Bloemen et al (127) where Dutch surgeons were asked about the technique they used for closing midline incisions, they found that very few followed the latest guidelines. Our conclusion is that structural implementation and education are essential when introducing a new surgical technique if one is to attain a long-lasting effect.

No significant differences in rates of incisional hernia, wound dehiscence, or surgical site infection before and after introduction of SSSB for abdominal closure were found in the retrospective study carried out at Capio St Görans Hospital. The study found that already 2010 – 2011 i.e., prior to introduction and implementation of SSSB, acceptable rates of incisional hernia and wound dehiscence existed. However, the structured implementation of the SSSB technique was not in vain since the use of a standardised technique enables quality follow-up and helps in the training of new surgeons. The SSSB technique is also a basic fundament of many new techniques that are currently introduced for treating burst and open abdomen.

4.3 INCIDENCE OF WOUND DEHISCENCE AND INCISIONAL HERNIA.

In the prospective randomised trials evaluating the SSSB technique, both Millburn (77) and Deerenberg (31) found high incidences of incisional hernia in their control arms where a large stitch technique was used. After implementation of the SSSB technique, the reported incidence was 5% and 13% respectively. Deerenberg et al used the EHS definition of incisional hernia where a defect seen on follow-up radiological examination, though not palpable, was considered a hernia. In their study, 47% of hernias were found by radiological examination only. This might explain the differences in incidences between these studies.

In the retrospective studies in this thesis, the incidence of incisional hernia was around 5%. This suggests that the surgical techniques used by most Swedish surgeons before the SSSB intervention at Capio S:t Görans hospital, were satisfactory. In these studies, only clinically evident incisional hernias were registered. As mentioned above about 50% of insicional hernias are asymptomatic and only found on focused examination or radiology (29,31,37). Karlsson et al reported an incisional hernia rate of 25% after colorectal cancer surgery in a study using postoperative CT scans for diagnosis (128). In their study, 12% of patients needed incisional hernia surgery. When extrapolating this to the present studies, the true incisional hernia rate in our cohorts would be expected to be at least 10%, which is still a level that is generally considered acceptable in terms of patient safety. When the EHS definition of incisional hernia is applied (4), clinical examination underestimates the incidence of incisional hernia. On the other hand, results from retrospective materials such as ours and the study by Walming et al (75) can be seen as an estimation of the rate of clinically relevant incisional hernia. In which case this should be about 5% in a Swedish setting with acute and emergency surgery.

Wound dehiscence is a rare complication of abdominal surgery. Kenig et al (51) and Webster et al (54) reported the incidence to be 2% and 3% respectively. Slater et al reported the incidence of wound dehiscence to be 0.4-1.2% in elective surgery and 12% in acute surgery (9). Tolstrup et al reported a decrease of the incidence of wound dehiscence from 7% to 4% after implemention of SSSB as standard technique for acute laparotomy (126). In prospective studies evaluating SSSB, the incidence of wound dehiscence, though not being an endpoint, was reported to be only 1% (31,77). In our initial prospective follow-up at S:t Görans hospital, we first saw the same tendency, but in the larger retrospective follow-up we found an incidence of 4%. In the register study based on SCRCR data, we found a reoperation rate for wound dehiscence of 2,9% (2,8% after elective surgery and 4,0% after acute surgery). Walming et al reported an incidence of 3,3% in a comparable retrospective study (75). Since wound dehiscence is a rare complication, a few cases only can lead to the difference in rates seen between different studies. There are also large differences in inclusion criteria in studies published. For example, Millbourn et al excluded all patients with repeat midline incisions. A fair assumption is that in current clinical practice the incidence of wound dehiscence after elective or acute surgery should not exceed 4%. Future studies on high risk patients should have the 4% level as their goal.

4.4 WOUND DEHISCENCE

Wound dehiscence normally leads to long hospital stay, reoperation, intensive care treatment, and often several reoperations. Our register-based study showed a significantly higher mortality risk for after reoperation for wound dehiscence. It was shown in both our retrospective studies that wound dehiscence patients face a high risk for incisional hernia. These findings were confirmed by Jensen et al who showed that wound dehiscence patients have higher mortality and a high risk for developing an incisional hernia (56). To summarise, I believe that in a hospital aiming at high quality, every case of wound dehiscence should be regarded as an adverse event and that an event analysis should be performed to see if anything could have been done pre-, peri- or postoperatively to prevent the event. For a midsize hospital such as S:t Görans Hospital with around 350 midline laparotomies per year, a reduction in the rate of wound dehiscence from 4% to 1% would save over one hundred hospital days a year and many acute operations.

4.5 RISK FACTORS FOR INCISIONAL HERNIA AND WOUND DEHISCENCE

In our studies, male gender, high BMI, and postoperative wound infection were found to be risk factors for incisional hernia and wound dehiscence.

Chronic obstructive pulmonary disease and generalised inflammatory disease were found to be statistically significant risk factors for wound dehiscence.

Age over 70 was found to be a risk factor for wound dehiscence but the risk for incisional hernia was lower.

Operation time less than 180 min was found to be a risk factor for wound dehiscence, and long operation time an independant risk factor for incisional hernia.

Wound dehiscence was a risk factor for incisional hernia.

The studies in this thesis showed that male gender is a risk factor for wound complications, though gender as a risk factor is disputed. Contrary to our findings, a study by Seo et al showed that female gender was a risk factor for incisional hernia (129) and in the Swedish Ventral Hernia Register, 58% of patients operated for incisional hernia were female (130).

From our studies there is strong evidence that high BMI increases the risk for incisional hernia and wound dehiscence. One theory is that truncal obesity, rather than high BMI itself, should be considered the risk factor for incisional hernia (83). Indeed, truncal obesity is more common in men, and may be the reason for the gender factor seen in our studies. Based on the findings in this thesis, I recommend considering men with a BMI>30 as having high risk for wound complications. I also believe that standardised measurement of perirenal fat on preoperative CT scans (measure of visceral obesity) combined with BMI would be a useful combination to identify patients at high risk.

Postoperative wound infection is another risk factor for incisional hernia and wound dehiscence. All possible measures should be undertaken to reduce the rate of wound infection, the most important being correct surgical technique. In the early phase of wound dehiscence there is serous discharge from the wound that may be misinterpreted as a wound infection. This could lead to antibiotic treatment and delay in diagnosing wound dehiscence, and also contribute to the strong association between wound infection and wound dehiscence/incisional hernia.

Postoperative surgical site infection is not a useful parameter for predicting complications. Furthermore, as surgical site infections are strongly associated with other wound complications, surgical site infection may act as confounder that obscures score-model assessment. Instead, future studies should focus on exploring risks associated with factors known preoperatively.

High age is a well-known risk factor for wound dehiscence and has also been recognised as a risk factor for incisional hernia in some studies. Our studies confirm that high age is a risk factor for wound dehiscence, whereas lower age was a risk factor for incisional hernia. Since the SCRCR does not include data from the primary healthcare service, this could be a source of bias in this thesis. Elderly patients with a subclinical incisional hernia are likely to be treated conservatively under the primary healthcare system and thus overlooked. We also know that 50% or more of incisional hernias are asymptomatic. With increasing age and reduced physical activity, this rate could be even higher. It is my opinion that high age should be taken into consideration in the preoperative assessment since it is a well-established risk factor for wound dehiscence. Patients with high age and comorbidity are the ones that are at great risk if they develop wound dehiscence or burst abdomen, and they might not be fit for reoperation. Prophylactic measures such as meticulous suturing and prophylactic mesh augmentation can be lifesaving in these cases.

In our studies based on SCRCR data, we found conflicting results regarding the role of operation time as a risk factor. That short operation time should be a risk factor for complication seems counter-intuitive. One explanation could be that palliative surgery and diagnostic surgery in critically ill patients may take less time though risk is high. A long operation time is a known a risk factor probably due to exhaustion of the surgeon or prolonged traction causing ischaemia in the abdominal wall. The patient also becomes exhausted and may not be fit enough for a relaparotomy. It would thus seem logical to take extra measures to prevent adverse events after a long operation.

The subgroup analysis found that acute surgery increases the risk for wound dehiscence but does not seem to significantly increase the risk for incisional hernia. This finding is congruent with previous findings (55,64). Because of the increased risk for wound dehiscence, acute surgery should be included when designing a risk score for complication after midline incision.

4.6 PROPHYLACTIC MESH AUGMENTATION AND TIGR® MATRIX MESH.

Prophylactic mesh placement to prevent incisional hernia in the high-risk patient is now a well-established procedure (131,132). There is also evidence that prophylactic onlay mesh can prevent wound dehiscence (133). In our study we found that onlay placed TIGR® Matrix mesh is safe and is a feasible way to reinforce the midline suture. TIGR® Matrix has also been tested as prophylaxis after open abdomen treatment (134). There are several possible advantages of using absorbable mesh material, but these must be tested in future trials.

4.7 THE SURGEON AS A RISK FACTOR.

Garcia-Urena et al (135) discuss in their review that some surgeons regard closure of the abdomen as “coffee time” and assign the task to an inexperienced junior colleague. Sometimes there is pressure to complete the list in time, that may lead to stress at the end of an operation. In other cases, the surgeon may be exhausted at the end of a demanding operation, or perhaps the patient is not properly relaxed causing difficulty in closing the abdomen. All these cultural issues need to be considered by hospitals aiming at high quality. Closure of the abdomen is as important for the patient as the main surgery.

All surgeons performing abdominal and pelvic surgery, not just general surgeons, need to be up to date on the importance of correct abdominal closure. Junior surgeons should be well supervised in closing the abdomen. The whole surgical organisation must be aware of the risk for incisional hernia so that individuals seeking to increase production consider the risk for complications associated with inadequate closure of the abdominal wall. Lists must be organised so there is time for meticulous suturing and prophylactic mesh augmentation. If the surgeon is exhausted, a well-rested colleague should be called in to help finish the operation. Good communication with the anaesthesiologist is crucial, so that the whole team understands the importance of abdominal wall suturing. Much suffering can be avoided and considerable savings for the healthcare system made if these simple principles are followed.

4.8 LIMITATIONS OF THE STUDIES

4.8.1 Paper 1

The intervention studied was not carried out with the aim of testing a scientific hypothesis, it was undertaken as a quality improvement project. As a result, there was no standardised follow-up protocol used in the study, instead it was performed retrospectively based on a review of medical records. Many patients visited the hospital only sporadically during the follow-up period, and patients were not examined in a strictly standard fashion. Incisional hernias in the study were diagnosed by either CT-scan or clinical examination during the follow-up period. Some of these hernias were asymptomatic. This limits comparison with other studies as well as the external validity of the study. Although all patients were followed throughout the study period, there was possible loss to follow-up if patients left the area or had their incisional hernia diagnosed at another department in Stockholm. In this retrospective study, many important parameters could not be analysed. One such clinically important risk factor that could have played a crucial role was smoking, since many medical records lack this information. To examine the effect of the SSSB technique more accurately, patients should have been followed-up prospectively using a standardised protocol. Wound dehiscence, on the other hand, is rarely neglected, and the rate of 3.7% found accurately reflects wound dehiscence when SSSB is used.

4.8.2 Paper 2

It is well-known that approximately 50% of incisional hernias are overlooked at clinical examination. In the present study, 5.3% of patients were diagnosed with incisional hernia or underwent hernia surgery, whereas the true incidence of incisional hernia probably exceeded 10%. Data from primary healthcare are not included in the registers used in this study, and there may have been patients that attended their GP with an asymptomatic incisional hernia that were never referred for surgical consultation. Exclusion of asymptomatic incisional hernias on the one hand allows focus on clinically relevant incisional hernias, but on the other hand prevents comparison with studies where the EHS definition of incisional hernia is applied (60). No association between comorbidity and risk for incisional hernia was seen. Patients with an incisional hernia deemed unfit for surgery could have been neglected in this analysis, thereby causing a selection bias. This could also explain why the rate of incisional hernia was higher in patients younger than 70 years. Most of the open procedures for colorectal cancer in this study were performed via a midline incision, but other approaches such as a transverse incision may have been used. The length of incision also varied and there was a mix of midline incisions above and below the umbilicus. These variations might bias the outcome of the study since they were not adjusted for. A drawback of this study is that there is no information about the surgical technique used to close the abdominal wall. During the study period 2007-2013, the implementation of SSSB gradually spread, and many Swedish colorectal cancer surgeons adopted the technique. The method of abdominal wall closure is still not included in the register, but if a similar study was repeated today, almost all patients would likely have their abdomen closed with the SSSB technique.

4.8.3 Paper 3

Surgery for colorectal cancer is performed on a heterogeneous group of patients, and includes acute, elective, curative, and palliative procedures. Most procedures are performed through a midline incision, but there could be cases in this cohort that underwent surgery using an approach with a lower risk for complications, e.g. transverse incision or Pfannenstiel incision. As in Study 2, the length and location of the incisions varied. The surgical technique used to close the midline incision probably affects the risk for wound dehiscence. The modern technique described by Milbourn et al was introduced in Sweden during the study period, but no specific data on surgical technique were available in the SCRCR. This limits the external validity of the study. More studies on wound dehiscence are needed, and these studies should use the SSSB technique for abdominal wall closure.

4.8.4 Paper 4

The present study was too small to provide evidence of the effectiveness of the technique and the new mesh material. Whether or not incisional hernias develop later when the mesh is completely resorbed can only be determined in studies with longer follow-up times and under tightly controlled circumstances. The present study was a pilot study in preparation for a larger randomised clinical trial, the Prevmesh trial, which is described below in “Future perspectives”. Three surgeons from three different hospitals performed the procedures. No surgeon found the procedure technically difficult or time-consuming. Fig 1 used in the article does not represent the correct technique described in the text and should not have been used.

5 CONCLUSIONS

Incisional hernia and wound dehiscence are serious and costly complications of abdominal surgery via a midline incision.

The Small-Stitch-Small-Bites technique for closing the abdominal wall lowers the risk for incisional hernia, but despite this, 5-10% of patients will develop an incisional hernia after open abdominal surgery.

Wound dehiscence is rare, but every case of wound dehiscence is a disaster for the patient. Wound dehiscence must be avoided at any cost.

High age, high BMI (especially visceral obesity), long operation time, acute surgery, chronic obstructive pulmonary disease, systemic inflammatory disease, and male gender are risk factors for wound complications after a midline incision.

Postoperative wound infection is a strong predictor of incisional hernia and wound dehiscence. All possible measures must be taken to avoid wound infection.

Structured implementation of a standardised surgical technique is possible and has a long-lasting impact on quality and outcome.

Onlay implantation of TIGR® Matrix mesh is a feasible way to reinforce the abdominal wall after surgery on high-risk patients.

6 FUTURE PERSPECTIVES

In the workup leading up to this thesis, a randomised controlled trial, PrevMesh, was planned and launched. The aim of the trial was to test the effectiveness of a prophylactic onlay TIGR® Matrix mesh on the incidence of incisional hernia and wound dehiscence. The study population comprised patients with high risk for postoperative wound complication undergoing surgery through a midline incision. The aim of the study was to include acute as well as planned procedures. Patients were to be randomised to two groups where the study group had the abdominal wall closed with the SSSB technique and reinforced with a TIGR® Matrix absorbable mesh. In the control group, the abdominal wall was to be closed with the SSSB technique but without mesh. PrevMesh was planned as a large multicentre trial including patients from large university hospitals to small rural hospitals. The study protocol is presented in Appendix 2, and more information about the study can be found at clinicaltrials.gov (Identifier: NCT02487134). Unfortunately, the study was paused before starting patient inclusion and the research question remains unanswered. Nevertheless, we intend to restart the study as soon as we have found sufficient funding.

Of all the studies referred to in this thesis, very few assume that the SSSB technique was used. Their results might thus be considered outdated. The HULC trial (136), comparing standardised closure using the SSSB technique to a study group where SSSB is used and the suture line is reinforced with a prophylactic mesh, is therefore long awaited. The HULC trial will include elective surgery only and excludes many risk factors for incisional hernia.

In future studies, patients at high risk of incisional hernia and wound dehiscence should be included. It may be assumed, for instance, that patients with a previous midline incision or previous ventral hernia repair would benefit even more from prophylactic mesh augmentation.

There are promising risk calculation models for incisional hernia and wound dehiscence, and these should be tested in prospective trials to see if they can help reduce these adverse events.

Another interesting field for future studies is prehabilitation. Howard et al use a standardised programme for patient preparation prior to surgery. In their study, patients showed a better physiological response to surgery and fewer complications after surgery (137). In a systematic review, Gillis et al concluded that nutritional prehabilitation with or without exercise decreases hospital stay after colorectal cancer surgery (138). Prehabilitation has also been tested on ventral hernia patients (139) where the prehabilitation group were less likely to suffer recurrence. Prehabilitation programmes prior to abdominal surgery should be the subject of further investigation as this might be one way to avoid adverse events.

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9 APPENDICIES

9.1 APPENDIX 1 EXAMPLE OF A3 TOOL

A3-mall

Datum och deltagare	Läkare Kirurgkliniken 12-05-25
Syfte och mål	Minska antalet Sårrupturer. Införa en standardiserad rutin för bukförslutning på sjukhuset.

Sammanfattning och bakgrund
Medellinjesnitt är förknippade med många komplikationer i form av sårrupturer, infektioner och ärrbråck. Frekvensen sårrupturer är större elektiva material c:a 4%, ärrbråck 20%. Genom en serie studier vid Länssjukhuset i Sundsvall-Härnösand och Umeå universitet har man tagit fram en metod att försluta buken som visat god evidens för färre komplikationer oberoende av övriga riskfaktorer hos patienten. Denna metod kan alltså användas på alla medellinjesnitt och minskar antalet vårdskador och reoperationer. Vid Länssjukhuset i Sundsvall-Härnösand har man idag en frekvens av 0,1% sårrupturer, 5% sårinfektioner och 5,6% ärrbråck.

Nuläge
Vid Mätning på operationer första halvåret 2011 på STG var frekvensen sårrupturer c:a 8-10% Det finns på sjukhuset ingent pm för bukförslutning utan var kirurg gör på sitt eget sätt.

Underliggande orsaker
Bukförslutning sker i slutet av operationen. Vid längre op/jourtid är man trött och kanske inte optimalt koncentrerad.

Mål och framtida plan
H. Strömberg producerar ett preliminärt PM för bukförslutning. Från och med 1/6-12 följa "sundsvallsmodellen" på prov 6 månader. Efter detta utvärdering och justering av pm:et Utbildningstillfällen under sommaren/hösten för läkare och op-personal så att alla känner till vetenskapen bakom metoden. Målet är att radikalt minska sårupturerna. Enl siffror från sundsvall borde StGöran inte ha mer än en vart fjärde år.

Handlingsplan för att nå målet		
Vad	Vem	När
Skriva PM Utbilda personal	Harald Strömberg Jonas Leo Åsa Öhrner	Utvärdering och beslut om PM klart 14/1-12

Uppföljningsplan	
Plan •Vad ska vi mäta? •När ska vi mäta? •Vem ska mäta?	Verkliga resultat •Hur blev utfallet jämfört med målet?

9.2 APPENDIX 2 LOCAL GUIDELINES ON OPENING AND CLOSING THE ABDOMINAL WALL (TRANSLATED)

Background*:*
Midline incisions are associated with severe complications such as wound dehiscence, wound infection, and incisional hernia. There is reliable evidence that the most effective way of reducing these complications is meticulous surgical technique.
Our department has decided, without exception, to use the so-called Sundsvall technique for closure of all midline abdominal incisions.

Opening:

- Spend time making your incision precisely in the midline. Apply the technique of subcutaneous fat fractioning if possible.
- Free the aponeurosis from subcutaneous tissue 1 cm on each side before it is incised, in preparation for closure.
- Use electrocautery to achieve clean aponeurosis edges for stitching.

Closure:

- Measure the incision length in the relaxed position. Use a ruler.
- Use PDS II 2-0, 150 cm, CT-1 needle.
- Suture length/wound length quote is measured by first measuring the incision length. The total length of the suture used minus the lengths cut off at the ends is assessed. Division of the suture length by the wound length gives the ratio.
- If the incision is longer than 30 cm you will need 2 sutures to reach a quote of at least 4.
- Use self-locking start and stop knots.
- Make sure to start at the very end of the incision.
- Start at the end of the incision and suture continuously using small bites 5-8mm from the aponeurosis edges. The interval between the stitches should be less than 5mm.
- Take bites in the aponeurosis only. Avoid mass layered sutures. If you leave the midline, take bites in the anterior rectus aponeurosis only.
- A low-tension suture is important, pull the suture so that the edges of the aponeurosis just adapt. The assistant should hold the suture without increasing the tension. The suture must be visible but the distance between the edges should be <10mm
- Suture length/wound length must be greater than 4, and the ratio must be measured and noted in the operation notes.
- If a ratio of four is not achieved, the suture must be redone. The ratio has no maximum.
- The theatre nurse has the responsibility to reach the surgeon a pair of scissors if a ratio of 4 is not achieved. If the surgeon choses to deviate from this routine, a non-compliance report must be made stating the reasons why.
- The skin must be closed with intracutaneous Monocryl® suture. If this is not possible, staples may be used.

References:

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9.3 APPENDIX 3

Study Protocol

Study Title: PrevMesh

A randomised study to compare routine abdominal wall closure with reinforcement using TIGR Matrix surgical mesh in the onlay position.

Version: 2.0

Date: 1 September 2017

Study Identification Number: SCRO194

Sponsor/Principal Investigator: Gabriel Sandblom, Centre for Gastric Surgery Disease, Karolinska University Hospital, Stockholm

Protocol signatures

Study title: PrevMesh -a randomised study to compare routine abdominal wall closure with reinforcement using TIGR Matrix surgical mesh in the onlay position.

Gabriel Sandblom, MD PhD	*Sponsor/ Coordinating Investigator*	*Date*
Fredrik Linder, MD	*Assisting Coordinating Investigator*	*Date*

1. DOCUMENT REVISION HISTORY

Edition	Date	Changes
1	2015-01-15	Initial version
2	2017-09-01	Changes include: Overall: New arrangement and administrative changes of the study protocol New title: PrevMesh -a randomised study to compare routine abdominal wall closure with reinforcement using TIGR Matrix surgical mesh in the onlay position. 5) Primary and secondary objectives: the objectives explained in more detail. 7) Study Procedures: clarified that the randomisation will be performed using randomisatio envelopes instead of electronic randomisation, changed eCRF system. Updated text on the blinding procedure. 9) Clinical assessments: follow-up visit at 3 years instead of 2 years. 10) Discontinuation criteria: new section that includes information that the patients are fre discontinue their participation in the study at any time, and that the patient can also be withdrawn from the study if medically necessary. 11)Data management: changed eCRF system and included more clarification about passwo etc. 12) Sample size estimation: 200 enrolled patients instead of the 400 in the initial protocol version. 14.1) Patient information and informed consent: more detailed information added. 14.3) Monitoring: since a monitor will perform site visits to monitor the eCRF data, this is clarified in the updated text. 14.4) Data protection and patience insurance: additional clarification 14.4) Suspension and early termination: new section 15) Investigator responsibilities: responsibilities clarified in more detail. Appendices A and B: new sections added. SF-36 replaced by RAND-36.

2. ABBREVIATIONS

CE-marked European Conformity-marked

eCRF	electronic Case Report Form
GCP	Good Clinical Practice
EC	Ethics Committee
IP	Investigational Product
QC	Quality Control
SAE	Serious Adverse Event
SADE	Serious Adverse Device Effect
SAP	Statistical Analysis Plan
SCRO	Scandinavian CRO

3. PROTOCOL SYNOPSIS

Rationale: Wound dehiscence and incisional hernias are common complications after major surgery. A wound dehiscence, i.e., rupture of the wound along the stitches in the fascia, may turn into complete dehiscence if the skin sutures also rupture and the abdominal contents protrude through the wall. Wound dehiscence can be lethal, especially in the elderly. It can lead to bowel lesions, infections, and organ failure. The risk of repeated wound dehiscence is also increased once dehiscence has occurred. The rationale of this study is to confirm patient benefit using a reinforcing surgical mesh in patients undergoing abdominal surgery.
Inclusion Criteria: • patients undergoing abdominal surgery • ≥2 risk factors (See Section 5.2.3 below) • Wound length >10 cm • Signed informed consent • Age ≥18 years Exclusion Criteria: • Presence of mesh after previous surgery • Presence of incisional hernia • Wound length <10 cm • Pregnancy • Age < 18 years • Infected wounds
Primary Objective: o To compare incisional hernia rates one year after surgery between the standard treatment group and reinforcing surgical mesh group. o To compare wound dehiscence rates one year after surgery between the standard treatment group and reinforcing surgical mesh group
Secondary Objectives: o To compare cumulative incisional hernia incidence three years and five years after surgery between the standard treatment group and reinforcing surgical mesh group. o To determine whether placing TIGR matrix surgical mesh in the onlay position is safe in routine clinical practice. o To compare seroma rates within one year and infection rates within one month after surgery, between the standard treatment group and reinforcing surgical mesh group o To compare numbers of patients with discomfort and/or persisting pain between the standard treatment group and reinforcing surgical mesh group after 30-days,one, three and five years. o To evaluate whether a resorbable TIGR.matrix mesh applied onlay reduces the risk for burst abdomen. o To perform a Health Economics evaluation to estimate the costs related to incisional hernia and burst abdomen (including a cost benefit estimation of placing a prophylactic resorbable mesh at laparotomy). o To describe the health-related quality-of-life status after laparotomy with and without placing a prophylactic mesh.
Study Design: Multicentre, parallel-group, randomised study on patients undergoing laparotomy.
Number of patients and sites: There will be 200 patients enrolled in the study, 100 patients in each group. Estimated number of participating sites: 4-10
Duration of the study: The study will begin August 2017, patient enrolment will carry on until Dec 2018. The study is scheduled to end Dec 2023.

4. INTRODUCTION

Wound dehiscence and incisional hernias are common? complications after major surgery. A wound dehiscence, i.e., rupture of the wound along the stitches in the fascia, may turn into complete dehiscence if the skin sutures also rupture and the abdominal contents protrude through the abdominal wall. Wound dehiscence can be lethal, especially in the elderly. It may lead to bowel lesions, infections, and organ failure. The risk for repeated wound dehiscence is also increased once a dehiscence has occurred.

Whereas a wound dehiscence develops during the initial healing phase, an incisional hernia occurs after the primary healing phase *i.e.*, after new peritoneum has developed. Due to incomplete healing, weakening of the abdominal wall may persist, leading to protrusion of the peritoneum and its contents. An incisional hernia may cause severe local symptoms and limit the ability to perform daily activities. If an incisional hernia incarcerates, it may become life-threatening. Techniques to repair incisional hernias do exist, but these repairs are very costly. Furthermore, an incisional hernia repair may lead to chronic pain and the functional results are seldom as favourable as after primary closure without hernia development.

Despite the fact the main risk factors for wound dehiscence have been identified and the technique for closing the abdominal wall has improved in recent years, the incidence of wound dehiscence after colorectal surgery is still 5-10 %. The measurable costs, including the costs for reoperation, prolonged hospital stay, and costs for other interventions are very high[1]. Measures to prevent wound dehiscence will be very cost-effective, reducing healthcare costs and improving health-related quality-of-life.

A way to prevent incisional hernias and wound dehiscence is to place a prophylactic mesh in the onlay position. This has been shown to radically decrease the risk for incisional hernia [2-4]. In a previous randomised study, it was shown that fixating a polypropylene mesh on the aponeurosis with 3 cm overlap on either side reduced the rate of incisional hernia within one year from more than 30% to less than 2 %[3]. There are, however, problems with leaving a mesh permanently in place, including seroma, infections, and persistent pain. A way to avoid this would be to reinforce the closure using a resorbable mesh so that any problems related to the mesh will eventually cease as the mesh is resorbed.

TIGR Matrix surgical mesh is a completely synthetic slowly resorbable mesh. It is knitted from two different synthetic resorbable fibres, possessing different degradation characteristics. The first fibre, making up 40% of the matrix by weight, is a copolymer of polyglycolide, polylactide, and polytrimethylene carbonate. The second fibre, making up 60% of the matrix by weight, is a copolymer of polylactide, and polytrimethylene carbonate. Both fibres degrade by bulk hydrolysis once implanted, resulting in a decreasing strength retention followed by mass loss of the fibres.

In a pilot study at three units in Sweden, TIGR Matrix surgical mesh was placed in the onlay position following procedures where the risk for postoperative burst abdomen or incisional hernia was considered to be high. The only mesh-related complication requiring treatment was a seroma in one patient, which was managed conservatively.

This investigation is a randomised controlled study to assess whether TIGR Matrix surgical mesh in the onlay position reduces the risk for burst abdomen and incisional hernia. Routine wound closure will be compared to the same routines but adding onlay TIGR Matrix surgical mesh.

5. STUDY OBJECTIVES

6. Primary Objectives

- To compare incisional hernia rates one year after surgery between the standard treatment group and reinforcing surgical mesh group.

- To compare wound dehiscence rates one year after surgery, between the standard treatment group and reinforcing surgical mesh group

7. Secondary Objectives

- To compare incisional hernia rates three and five years after surgery between the standard treatment group and reinforcing surgical mesh group.
- To determine whether placing TIGR matrix surgical mesh in the onlay position is safe in routine clinical practice.
- To compare the incidence of seroma within one year and infections within one month after surgery
- To compare the numbers of patients with discomfort and/or persistent pain between the standard treatment group and reinforcing surgical mesh group after 30-days,one, three, and five years.
- To evaluate whether onlay resorbable TIGR matrix surgical mesh reduces the risk forburst abdomen.
- To perform a Health Economics evaluation to estimate the costs related to incisional hernias and burst abdomen (including a cost benefit estimation of placing a prophylactic resorbable mesh at laparotomy).
- To describe the health-related quality-of-life status after laparotomy with and without placing a prophylactic mesh.

8. STUDY DESIGN

A randomised, multicentre study aimed to compare the risk for incisional hernia and burst abdomen between patients who undergo prophylactic reinforcement of the aponeurosis with onlay TIGR matrix surgical mesh and patients undergoing wound closure according to established routines.

9. Selection of Study population

Patients planned for elective surgery via a midline incision for colon or rectal cancer will be screened for this study. Included are:

- Patients undergoing emergency surgery? with an abdominal midline incision for peritonitis, intestinal obstruction and other diagnoses.
- Patients planned to undergo other types of abdominal incision? (transverse incision, subcostal incision, large T-type incisions (“Mercedes incision”) or a large incision combined with midline and transverse divisions of the abdominal wall.

10. Inclusion and Exclusion Criteria

The inclusion and exclusion criteria for enrolling patients in this clinical investigation are the following:

11. Inclusion Criteria

- patients undergoing abdominal surgery
- ≥2 risk factors (See Section 5.2.3 below)
- Wound length >10 cm
- Signed informed consent

12. Exclusion criteria

- Presence of mesh after previous surgery
- Presence of incisional hernia
- Wound length <10 cm
- Pregnancy
- Age < 18 years
- Infected wounds

13. Risk factors for wound dehiscence and incisional hernia

- Reoperation
- Age over 80 years
- Generalised malignant decease (presence of distant metastases at the time of surgery)
- COPD (Chronic obstructive pulmonary disease). Grades III-IV according to the GOLD classification (FEV1 < 50% of the expected)
- Serum Albumin level <20 g/l
- Sepsis. Infection in combination with two or more of the following: abnormal body temperature, heart rate, respiratory rate or blood gas, and white blood cell count.
- BMI 35-45 (for patients with BMI>45, no additional risk factors are required for inclusion)
- Haemoglobin <80 g/l
- Diabetes with secondary complications (angiopathy, nephropathy, or neuropathy) and insulin treatment
- Steroid treatment (with at least 1 mg betamethasone daily or equivalent) for 7 days preoperatively
- Smoking (at least 10 cigarettes a day for one year)
- Chemotherapy (last administration within 2 weeks prior to surgery
- Radiation to the abdominal wall

14. STUDY PROCEDURES

15. Randomisation procedure

Patients who fulfil the inclusion criteria with none of the exclusion criteria are invited to participate in the study prior to surgery.

The Investigator will be responsible for the verbal and written patient information and for obtaining informed consent from each patient. The screening section in the eCRF will be completed, if worksheets are used instead, the eCRF must be filled in later. The randomisation procedure will be carried out after closure of the fascia, by opening a randomisation envelope (located in the site master file). The envelope contains a note stating whether patient is randomised to wound closure of the abdominal wall according to ordinary routine with fascial sutures, or closure with fascial sutures according to ordinary routine plus the addition of TIGR matrix surgical mesh applied onlay. An independent biostatistician not involved in other aspects of the study will be responsible for the preparation of randomisation envelopes.

Postoperative management is the same in both groups and adapted to local routines and the specific procedure the patient has undergone. Since postoperative complications related to the mesh may occur, there will be no blinding of the investigators and study staff, but patients should not be informed about the which treatment arm they are randomised to.

16. Wound closure

In cases where the patient is randomised to the TIGR Matrix surgical mesh group and antibiotics have not been given for any other indication, peroperative 1.5 g Cefuroxim intravenously (iv) will be given peroperatively as prophylaxis. In cases where the patient does not tolerate Cefuroxim, 600 mg Clindamycin iv will be given instead. Prophylactic antibiotics given will be registered. The same principles for wound closure will be applied in both groups[5]. The aponeurosis will be closed with continuous PDS 2/0 sutures and self-locking anchor knots. The stitches will be placed 5-8 mm from the wound edge, 4-5 mm apart. The suture to wound length ratio will be recorded.

If the patient is randomised to placement of TIGR Matrix surgical mesh, the subcutaneous tissue will be dissected from the aponeurosis 4 cm on either side of the incision as well as in cranial and caudal directions. A TIGR matrix surgical mesh 7 cm wide and 6 cm longer than the incision will be placed onlay and fixated with continuous PDS 2/0 stitches to the aponeurosis on either side of the incision. The stitches fixating the aponeurosis should be placed with an interval of 10 mm.

The time required to close the abdomen, including closing the midline incision and, if applicable, placement of the mesh, will be registered.

17. Visit schedule

	Screening/ Baseline	Discharge from hospital	1 month	1 year	3 years	5 years
Inclusion Criteria	X					
Exclusion Criteria	X					
Informed Consent	X					
Follow-up outpatient visit			X	X	X	X
CRF Completion	X	X	X	X	X	X
Fill in RAND-36			X	X	X	X
Ventral Hernia Pain Questionnaire[6]			X	X	X	X
Adverse Event Assessment		X	X	X	X	X
Computer tomography				X		

18.

19.

20.

21.

22. INVESTIGATION PRODUCT (IP)

TIGR® Matrix Surgical Mesh is a CE-marked medical mesh knitted from two different synthetic resorbable fibres possessing different degradation properties. The first fibre, making up 40% of the matrix by weight, is a copolymer of polyglycolide, polylactide, and polytrimethylene carbonate. The second fibre, making up 60% of the matrix by weight, is a copolymer of polylactide, and polytrimethylene carbonate. Both fibres degrade by bulk hydrolysis once implanted, resulting in a decreasing strength retention followed by mass loss of the fibres. Based on the product's absorption characteristics, *in vitro* testing showed that the first fibre (polyglycolide, polylactide, and polytrimethylene carbonate) loses its functional capabilities after 2 weeks and *in vivo* studies in the abdominal wall of sheep showed that the first fibre was fully absorbed after 4 months. The same *in vitro* testing showed that the

second fibre (polylactide, and polytrimethylene carbonate) loses its functional capabilities after 9 months and *in vivo* studies in the abdominal wall of sheep indicated that the second fibre should be absorbed after approximately 36 months. TIGR Matrix Surgical Mesh, is a resorbable mesh implant, classified as a Class III device in accordance with the European Medical Device Directive (MDD) 93/42/EEC, Annex IX, Section 2.4, Rule 8.

23. CLINIAL ASSESSMENTS

24. Screening/Baseline assessment

The following variables are registered in the eCRF:

- Birth Year
- Gender
- Length (cm)
- Weight (kg)
- BMI
- Inclusion/Exclusion criteria fulfilled
- Medical history and concurrent diseases
- Prior and concomitant medication/treatment
- Physical examination
- Preoperative risk factors (≥2 risk factors essential)
- Indication for surgery including ICD-code
- Incision and suture length, and length ratio
- Time from start of fascia closure to end of mesh suture
- Degree of wound contamination according to the American College of Surgeons

25.

26. Follow-up assessments

A clinical follow-up visit will be made at 30-days, one year, three years, and five years after surgery. At the follow-up visits, all patients will be monitored for signs of infection, wound rupture, incisional hernia, subcutaneous seroma, and postoperative symptoms. Other adverse events related to the IP and serious adverse device effects (SADE) will be registered as well as any serious complications that could be related to the presence of the mesh. Patients will also be requested to fill in RAND-36 (Appendix A) and the item worst pain last week from the Ventral Hernia Pain Questionnaire[6] (Appendix B). A computer scan one year after surgery will also be included in the follow-up schedule.

The patients are not allowed to participate concurrently in any other clinical investigation concerning abdominal wall closure.

If more than three serious complications related to the mesh are registered, a data safety committee will determine if the study should be interrupted or not.

27. DISCONTINUATION CRITERIA

Patients are free to discontinue participation in the clinical investigation at any time. A patient can also be withdrawn from the clinical investigation if, in the opinion of the investigator, it is medically necessary. If isolated visits are not attended, this is not a reason to withdraw the patient. If a patient does not return for a scheduled follow-up visit, the investigator will make reasonable efforts to contact the patient. Whatever, every effort should be made to document patient outcome. For patients who are withdrawn, the date of withdrawal from the clinical

investigation and the reason for withdrawal will be recorded in the eCRF (e.g. lost to follow-up, consent withdrawn, protocol violation, SADEs etc). All evaluations scheduled for the final clinical investigation visit should be completed as soon as possible after the patient is withdrawn from the clinical investigation. Withdrawn patients should not be re-entered into the clinical investigation.

28. DATA MANAGEMENT

Data management based on Good Clinical Practice (GCP) refers to the activities defined to achieve safe routines for entering patient information into a database, avoiding errors.

The data management routines include procedures for handling of e-CRF, database set-up and management, data entry and verification, data validation, quality control (QC) of database, and documentation of the performed activities including information of discrepancies in the process. The database, data entry screens, and programme will be designed in accordance with the Study Protocol by Scandinavian CRO.

Clinical data will be entered into an eCRF. The eCRF includes password protection and internal quality checks, such as automatic range checks, to identify data that appear inconsistent, incomplete, or inaccurate.

The site investigator must verify that all data entries in the eCRF are accurate and correct. This is done with an investigator signature for each patient's CRF data set. Sites will also be monitored, see section 12.3. The eCRF used in this study will be "Trial on-line".

29. SAMPLE SIZE ESTIMATION

Patients with at least two risk factors are expected to have a risk of at least 10 % to develop an incisional hernia after one year if no prophylactic mesh is used[7]. If a prophylactic mesh reduces this risk to 1.5% one year after surgery, 90 patients in each group with complete data are required to achieve an 80% chance of detecting a difference at the $p<0.05$ level. To compensate for 10 % dropout and death before end of follow-up, the goal is to include a total of 100 patients in each group.

Estimated number of participating sites: 4-10

30. STATISTICS PLAN

Statistical study analyses will be performed after the study is completed and the database is released. All statistics, including tables, figures, and listings, will be performed using SAS®, version 9.2 or higher. The statistical analyses will be described in detail in the Statistical Analysis Plan (SAP) which will be finalised and approved before database lock.

31. Descriptive Statistics

All data will be presented using descriptive statistics. Results will be presented in total and by treatment group. Continuous variables will be summarised using number of patients, mean, standard deviation, median, minimum and maximum. Categorical variables will be summarised using the number and percentage of patients. The full analysis set is defined as all randomised patients who had a placement of TIGR Matrix surgical mesh.

32.

33. Primary Endpoints

- incisional hernia one year after surgery
- wound dehiscence one year after surgery

34. Secondary Endpoints

- incisional hernia three years and five years after surgery
- incidence of seroma within one year
- infections within one month after surgery
- wound dehiscence 1 months after surgery
- RAND-36
- VHPQ

35. ADMINISTRATIVE AND REGULATORY REQUIREMENTS

36.

37. Patient Information and Informed Consent

Inclusion in the study requires oral and written consent. It is the responsibility of the Site Investigator to give each patient adequate verbal and written information regarding the objectives and the procedures of the study as well as any risks or inconvenience involved before including the patient in the study. The patient should be informed that by signing the informed consent form, he/she authorises monitor(s), auditor(s), and the EC to have direct access to their medical records for verification of clinical study procedures. The patient must be informed about the right to withdraw from the study at any time. The patient should be allowed sufficient time for consideration of the proposal.

In signing the consent form, the patient or his/her legal representative shall

- agree to participate in and comply with the clinical investigation,
- agree to his/her personal physician being informed of his/her participation, or state his/her refusal to release of this information,
- agree to the use of his/her relevant personal data for the purpose of the clinical investigation.

The signed informed consent forms must be filed by the Site Investigator for possible future audits and/or inspections. The final version of the patient information and informed consent forms will be submitted to the EC and must not be changed without permission from the Sponsor.

38.

39. Approval from Ethics Committee and the Radiation Safety Authority

Approval from the Ethics Committee (EC) will be obtained. Any substantial amendment(s) that arise(s) during the study will be submitted for approval to the same EC. Furthermore, as patients will undergo computer tomography, approval will be obtained from the Swedish Radiation Safety Authority.

40.

41. Monitoring

The Site Investigator at each unit is responsible for assuring that the principles of GCP are followed. However, monitoring visits to each investigational site will be conducted by the assigned monitor as described in the monitoring plan. The investigator will allow the monitor to inspect the clinical facilities to assure compliance with GCP. The CRFs and patient's corresponding original medical records (source documents) are to be fully available for review by the monitor at regular intervals. These reviews verify adherence to study protocol and data accuracy in accordance with federal regulations and local regulations. A monitor from Scandinavian CRO (SCRO) will carry out all monitoring activities.

42. Data Protection and Patience Insurance

For data protection purposes, the sponsor and the Site Investigators will ensure the confidentiality of the data of the study participants. Personuppgiftsansvarig for this study is Karolinska Universitetssjukhuset.

The patients will be informed that their personal identity information will be replaced by a code "subject study number". The investigator will keep a link (ID-log) that identifies a patient to his/hers coded information, but this link will be kept secure and available only to the investigator or selected members of the research team (this list should be preserved for monitoring and/or possible future inspections/audits).

Any information that can identify a patient will remain confidential. Any personal information that could identify a patient will be removed or changed before files are shared with other researchers or results are made public. The Swedish regulations for the handling of computerised data will be followed throughout the study.

43. Suspension or early termination of the clinical investigation

If an investigation is terminated prematurely or suspended, the sponsor shall promptly inform the clinical investigators/investigation centres of the termination or suspension and the reason(s) for this.

The Ethics Committee shall also be informed promptly and provided with the reason(s) for the termination or suspension by the sponsor or by the clinical investigator/investigation centres.

44. INVESTIGATOR RESPONSIBILITIES

The clinical investigator shall be responsible for the day-to-day conduct of the clinical investigation as well as for the safety and well-being of the human patients involved in the clinical investigation. The clinical investigator shall:

- make sure that the study protocol is followed by all responsible for the conduct of the clinical trial
- ensure that the patient has adequate information to give informed consent
- ensure that informed consent is obtained and documented
- have primary responsibility for the accuracy, legibility, and security of all clinical investigation data, documents and patient records at his investigation site both during and after the clinical investigation.

- support the monitor and auditor, if applicable, in their activities to verify compliance with the study protocol, to perform source data verification and to correct the CRF where inconsistencies or missing values are identified.

45. QUALITY ASSURANCE

The study will be conducted in accordance with GCP. All study procedures will be performed according to the study protocol and will be documented appropriately.

46. REFERENCES

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7. Itatsu K, Yokoyama Y, Sugawara G, Kubota H, Tojima Y, Kurumiya Y, Kono H, Yamamoto H, Ando M, Nagino M. Incidence of and risk factors for incisional hernia after abdominal surgery. Br J Surg 2014 Oct: 101 (11):1439-47

47. APPENDIX A RAND-36 Questionnaire

RAND-36 Hälsa och livskvalitet

RAND-36 handlar om din hälsa och funktion i vardagen. Välj det svarsalternativ som stämmer bäst för dig på varje fråga

	Utmärkt	Mycket god	God	Någorlunda	Dålig
1. I allmänhet, skulle du säga att din hälsa är:	☐	☐	☐	☐	☐

	Mycket bättre	Något bättre	Ungefär densamma	Något sämre	Mycket sämre
2. **Jämfört med för ett år sedan,** hur skulle du bedöma din hälsa **nu**?	☐	☐	☐	☐	☐

Följande frågor handlar om aktiviteter du kan tänkas ägna dig åt en vanlig dag. **Begränsar din nuvarande hälsa dig** i dessa aktiviteter? Om ja, hur mycket?

	Ja, mycket begränsad	Ja, lite begränsad	Nej, inte alls begränsad
3. **Fysiskt ansträngande aktiviteter**, t.ex. löpning, lyfta tunga föremål, delta i ansträngande idrotter	☐	☐	☐
4. **Måttligt ansträngande aktiviteter**, t.ex. flytta ett bord, dammsuga, promenera eller cykla	☐	☐	☐
5. Lyfta eller bära matkassar	☐	☐	☐
6. Gå upp för **flera** trappor	☐	☐	☐
7. Gå upp för **en** trappa	☐	☐	☐
8. Böja dig eller gå ner på knä	☐	☐	☐
9. Gå **mer än ett par kilometer**	☐	☐	☐
10. Gå **flera kvarter** (flera hundra meter)	☐	☐	☐
11. Gå **ett kvarter** (hundra meter)	☐	☐	☐
12. Bada/duscha eller klä på dig	☐	☐	☐

Under de **senaste 4 veckorna**, har du haft något av följande problem med ditt arbete eller andra vanliga dagliga aktiviteter **på grund av din fysiska hälsa**?

	Ja	Nej
13. Dragit ner på **tiden** du ägnat åt arbete eller andra aktiviteter	☐	☐
14. **Fått mindre gjort** än du skulle vilja	☐	☐
15. Begränsats i **vissa** arbetsuppgifter eller andra aktiviteter	☐	☐
16. Haft **svårt** att utföra arbete eller andra aktiviteter (t.ex. det krävdes mer ansträngning)	☐	☐

Under de **senaste 4 veckorna**, har du haft något av följande problem med ditt arbete eller andra vanliga dagliga aktiviteter **på grund av känslomässiga problem** (t.ex. att du känt dig nere eller orolig)?

	Ja	Nej
17. Dragit ner på **tiden** du ägnat åt arbete eller andra aktiviteter	☐	☐
18. **Fått mindre gjort** än du skulle vilja	☐	☐
19. Utfört arbete eller andra aktiviteter mindre **noggrant** än vanligt	☐	☐

	Inte alls	Lite grand	Måttligt	Ganska mycket	Extremt mycket
20. Under de **senaste 4 veckorna**, i vilken omfattning har din fysiska hälsa eller känslomässiga problem stört dina vanliga sociala aktiviteter med familj, släkt, vänner, grannar eller föreningar etc.?	☐	☐	☐	☐	☐

	Ingen	Mycket lätt	Lätt	Måttlig	Svår	Mycket svår
21. Hur mycket **fysisk** smärta har du haft under de **senaste 4 veckorna**?	☐	☐	☐	☐	☐	☐

	Inte alls	Lite grand	Måttligt	Ganska mycket	Extremt mycket
22. Under de **senaste 4 veckorna**, hur mycket har smärta stört ditt vanliga arbete (gäller både arbete utanför hemmet och hushållsarbete)?	☐	☐	☐	☐	☐

Följande frågor handlar om hur du känner dig och hur det har varit **under de senaste 4 veckorna**. Ange det svar som stämmer bäst med hur du känt dig.

Hur mycket av tiden under de **senaste 4 veckorna** ...	Hela tiden	Största delen av tiden	En stor del av tiden	En viss del av tiden	En liten del av tiden	Inget av tiden
23. Har du känt dig pigg?	☐	☐	☐	☐	☐	☐
24. Har du känt dig mycket nervös?	☐	☐	☐	☐	☐	☐
25. Har du känt dig så nere att ingenting kunnat muntra upp dig?	☐	☐	☐	☐	☐	☐
26. Har du känt dig lugn och harmonisk?	☐	☐	☐	☐	☐	☐
27. Har du känt dig energisk?	☐	☐	☐	☐	☐	☐
28. Har du känt dig dyster och ledsen?	☐	☐	☐	☐	☐	☐
29. Har du känt dig utsliten?	☐	☐	☐	☐	☐	☐
30. Har du känt dig lycklig?	☐	☐	☐	☐	☐	☐
31. Har du känt dig trött?	☐	☐	☐	☐	☐	☐

	Hela tiden	Största delen av tiden	En viss del av tiden	En liten del av tiden	Inget av tiden
32. Under de **senaste 4 veckorna**, hur mycket av tiden har din **fysiska hälsa eller känslomässiga problem** stört dina sociala aktiviteter (som att träffa vänner, släktingar etc.)?	☐	☐	☐	☐	☐

Hur väl stämmer följande påståenden in på dig?

	Stämmer helt	Stämmer ganska bra	Vet inte	Stämmer ganska dåligt	Stämmer inte alls
33. Jag verkar ha något lättare att bli sjuk än andra människor	☐	☐	☐	☐	☐
34. Jag är lika frisk som andra jag känner	☐	☐	☐	☐	☐
35. Jag tror att min hälsa kommer att försämras	☐	☐	☐	☐	☐
36. Min hälsa är utmärkt	☐	☐	☐	☐	☐

48. APPENDIX B VHPQ Questionnaire

Patient will assess worst perceived pain the past week according to a VHPQ item. The following question will be asked “Gradera smärtan i magen då den var som värst under senaste veckan?”

- Ingen smärta
- Smärta som lätt har kunnat ignoreras
- Smärta som inte har kunnat ignoreras, men som inte påverkat dina vardagsaktiviteter
- Smärta som inte har kunnat ignoreras, och som påverkat koncentrationen på sysslor/aktiviteter
- Smärta som har förhindrat de flesta aktiviteter
- Smärta som har krävt vila/sängläge
- Smärta som har varit så svår att du var tvungen att söka omedelbar hjälp